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OXYGENATION AND RETROLENTAL FIBROPLASIA*

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THE causative factors of disease may be broadly grouped under three headings: those due to injurious agents, those resident in the susceptible host and those deriving from the environment in which host and agent find themselves[1]; clarification of causation is to be sought along "a broadened front on which the laboratory and the clinic or the field have been brought together for interpretation of a problem."[2] These principles guide the search for causes of a noncommunicable illness like retrolental fibroplasia (RLF) no less than that for viruses of infantile paralysis, for example; investigation proceeds in the clinic, field and laboratory. Research studies of a decade have brought medical attention to focus gradually on abnormal states of oxygenation as primary incitants of RLF; on the underdeveloped capillary network of the fetal retina as a contribution of the prematurely born fetus; and on multiple chemical, physical and social factors in the extrauterine environment (even economic influences such as number and kind of oxygen tents). The term fetus rather than infant is used advisedly because the conceptus that is expelled prematurely from the uterus and made to survive in an incubator is still a fetus developmentally, quite as much as if it were still enveloped by an amnion and nourished and oxygenated from a placenta.

It becomes increasingly clear that an optimal oxygen supply — neither too little nor too much — is necessary for normal development of the vascular system and that one must take into consideration a variable dosage factor involving concentrations of oxygen starting at next to nothing (anoxia, hypoxia) and increasing through the normal 20 per cent level in ambient air at sea level to 60 to 80 per cent atmospheres (hyperoxia) attainable in tents and specially constructed incubators. Not only is the environmental oxygen of major importance but also the duration, timing and suddenness of changed tensions. An evaluation of the importance of oxygen lack or excess in respired air and in the tissues can only be made against the general background of normal systemic, pulmonary and hematologic development and the particular background of ocular structure and function. The vascular network of the retina of the fetus in the seventh and eighth months after conception is differentiating so rapidly that it becomes a determining force in the final expression of RLF.[3-5] Additional host factors that are assuredly of importance include red-cell numbers and hemoglobin concentrations,[6] enzyme and electrolyte patterns[7,8] body temperature and humidity.[9]

CLINICAL AND PATHOLOGICAL DEFINITION

RLF is the end result of an angioblastic outgrowth into the vitreous of fine capillary vessels deriving from the vascular tree of the developing retina.[10] The first manifestations occurring in the early months of extrauterine life, which were defined by Owens and Owens,[11] are functional changes — congestion and tortuosity of retinal vessels, ordinarily in a prematurely born infant of such precariously low birth weight that it is reared in the premature nursery of the modern lying-in hospital. Over a period of weeks, edema and hemorrhage are observed in the fundus,[12] constituting structural changes that may completely regress or proceed to the cicatricial phase of RLF[13] if the child survives. In the eyes of infants with early cicatricial manifestations of RLF at autopsy Heath[10] noted hemorrhages, edema, and vascular proliferations on the surface of and within the retina. He observed a delicate haze or cloud of "countless minute, hairlike fibrillae" in the vitreous and added, "When the mistlike fibrillae . . . have developed to the point of organization and the retina is partially separated the process cannot reverse." As the clinical disease advances progressive clouding of the vitreous and formation of an opaque retrolental membrane occur in association with partial or complete separation of the retina. In the advanced stages of RLF, as first described by Terry[14,15] and confirmed by Krause[16] and Reese and Payne[17] and as illustrated in color by Reese and Blodi,[18] a variable mass of contracting scar tissue in the vitreous explains the partial or complete blindness that is the ultimate expression of the condition.

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Etiology

Zacharias,[19] in an excellent review of RLF, has given an account of the evolution of medical opinion on the importance of various physical, chemical and microbiologic agents suggested as possible causes by Terry,[20] Reese and Payne,[17] Kinsey and Zacharias[21] and others.[22-26] Nutritional deficiencies and excesses, irritation from light, dehydration and electrolyte disturbances consequent to blood transfusion have been successively studied as possible causes, but without evidence that any one of these complexes has determined the almost epidemic prevalence of the condition among markedly premature infants in late years. Gradually, the focus of medical scrutiny has come to rest on the state of oxygenation of the premature infant in the neonatal period. Accessory etiologic factors and mechanisms are, however, of undoubted importance.

In 1948 Ingalls[27] reported 33 cases of RLF in prematurely born infants. In 1 the signs of hypoxia antedated birth, and this infant had prune-juice-colored spinal fluid in the first week of life, interpreted as the result of intracranial bleeding in utero due to anoxemia three weeks before delivery when the mother had had gross hemorrhage from placenta praevia; another baby was born prematurely after the mother suffered a respiratory infection in the seventh month of gestation, with severe coughing, rupture of a placental vessel and such severe hemorrhage that cesarean section was necessary. On the basis of such clinical evidence and the mass data of Terry,[20] Krause[16] and Reese and Payne[17] — data indicating a high rate of multiple births, toxemia of pregnancy, placental disease and hemorrhage among the mothers of 41 infants in whom RLF developed — the inference was drawn that lack of oxygen to the fetus was the most important cause of permanent damage of vascular tissues, special features of the clinical syndrome being due to the stage of development of the host at the time the injurious agent acted. Such a theory harmonized with Krause's[16] conception of RLF as a systemic "pathologic entity" rather than a strictly localized, ocular process, but the great difficulty of the interpretation was the widespread continued and even increasing incidence of the disease in 1949 and 1950 in many nurseries best endowed with oxygen equipment.

The hypothesis that hypoxia was active in causing RLF received support from the histologic studies of Klien[28] and the clinical experience of Rudolph and Sirlin,[29] as well as the laboratory experiments of Ingalls and his associates.[30-32] However, a contrary point of view soon developed when the very measure — the use of oxygen in incubators — that would be expected to relieve the effects of hypoxia began to be suspected of being a possible cause of RLF. In May, 1951, Lelong and his co-workers[33] suggested from clinical experience that hyperoxia rather than anoxia might be the prime factor, adding that they were convinced of the necessity of revising their procedure on this point so as to define more strictly the indications for oxygen and to apportion its application more exactly. This view was given support in July of the same year by the finding of K. Campbell,[34] of Melbourne, Australia, that RLF developed in 23 (18.7 per cent) of 123 prematurely born infants maintained in atmospheres containing 40 to 60 per cent oxygen; only 4 (7.0 per cent) of 58 prematurely born infants given no supplemental oxygen unless by catheter or face mask acquired the disease.

In December the preliminary observations of Szewczyk[35] provided the rationale for examining the two extreme positions as possibly related parts of the etiologic complex. Nine infants with early signs of RLF improved within a day or two when placed in an atmosphere of 60 to 70 per cent oxygen, whereas early signs of RLF were induced in 7 premature infants previously maintained in high concentrations of oxygen (50 per cent) when they were abruptly removed to room air. Szewczyk's[36] main report was published in March, 1952, along with others by Ryan[37] in support of Campbell's hypothesis of a "toxic" effect of oxygen, and by Ingalls, Tedeschi and Helpern,[32] who induced vasoformative tissue in the retrolental space by subjecting the pregnant mouse to hypoxia. Szewczyk observed that when infants acclimated to 50 per cent oxygen over a period of several days were abruptly withdrawn to ordinary levels (22 per cent) in room air, the retinal vessels dilated and hemorrhage and edema of the retina appeared within a few days. When the same babies were returned to high oxygen concentrations, prompt regression of the condition was noted. These changes were interpreted as resulting from inadequate oxygenation of the blood induced by exposure of a premature infant to an environment of higher oxygen concentration and withdrawing him so rapidly that the physiologic changes of acclimatization could not take place before rapidly differentiating areas such as the retina of the eye had been harmed. Szewczyk[36] concluded: "What we are actually witnessing with our ophthalmoscopes in the study of this disease is the response of immature neural tissue to slight anoxia." These observations were confirmed by Jefferson,[38] who found that vascular engorgement abated within forty-eight hours when 6 infants with early changes of RLF who had been removed from oxygen tents to room air were returned to high tensions of oxygen.

Disputing the interpretation of Szewczyk and Jefferson, Patz, Hoeck and De La Cruz[39] emphasized the direct toxicity of oxygen in high concentrations to retinal vascular tissue. In a study undertaken to evaluate the role of oxygen therapy in the pathogenesis of RLF they followed two groups of premature infants alternately assigned to a high oxygen (65 to 70 per cent) environment for a period of four to seven weeks and to one of low oxygen concentration (under 40 per cent) for less than two weeks. Seven

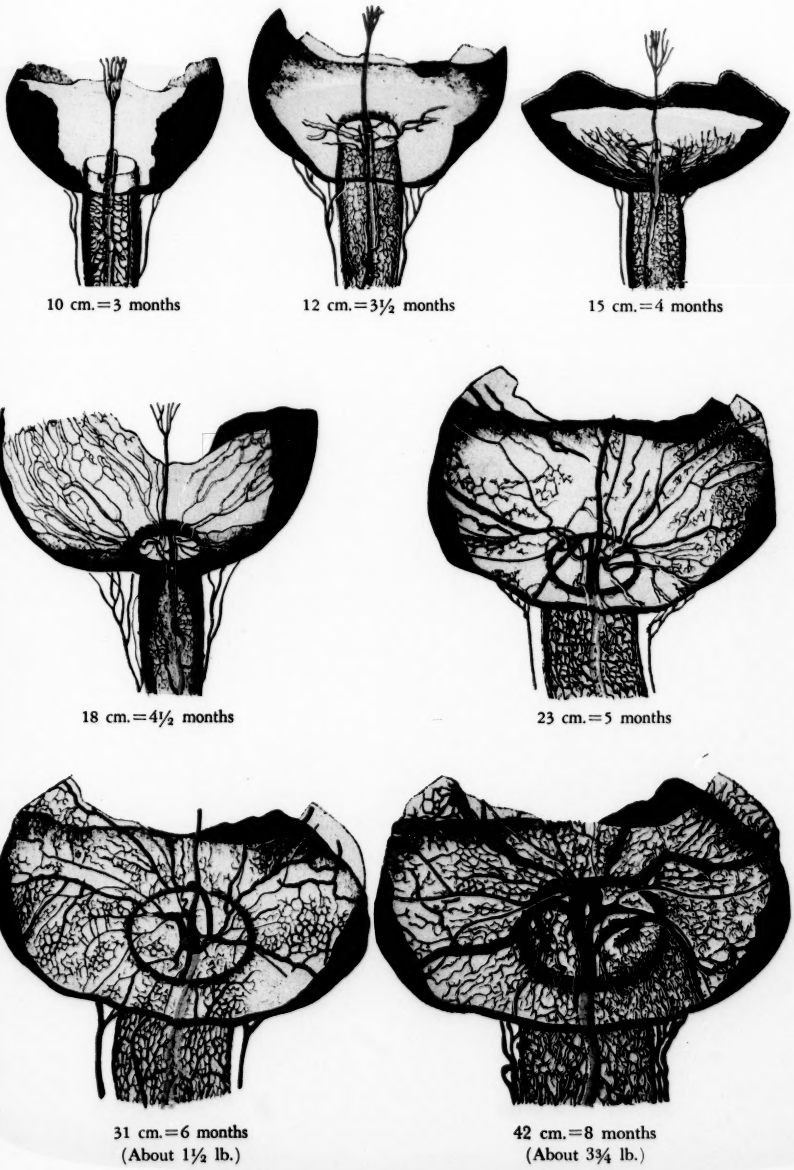

FIGURE 1. *Development of Vascular System of the Eye in the Human Fetus (after Versari[2]).*

of 28 infants in the group exposed to high oxygen atmospheres progressed to cicatricial stages of RLF; among 37 in the other group these irreversible forms of the disease did not develop. Since the ocular lesions occurred in some cases while infants were still in the incubators, the authors favor a toxic effect of oxygen as the prime cause of RLF.

So many studies incriminating the incubator in the etiology of RLF have since been published that the significance of its role appears to be established. It is not yet settled whether the etiologic mechanism is to be viewed as a relatively simple toxic effect of hyperoxia or to a more complex one involving body-temperature fluctuations, electrolyte shifts, hemoglobin concentration, sudden changes from one atmosphere to another and, ultimately, hypoxia. The argument in favor of a more complex mechanism and of a chain of circumstances ultimately leading to retinal hypoxia is strong[30,31,35,37,38,40-42] but not proved. On the other hand neither the clinical evidence of Patz and his associates nor the experimental production of neovascularization of the retina in kittens exposed to 80 per cent oxygen by Ashton, Ward and Serpell[43] clinches the case for direct oxygen toxicity. As Himwich[42] and others[44-47] have pointed out, the carrying power of the blood for carbon dioxide is diminished during inhalation of oxygen at excessive pressures; this in turn brings on an acidosis that may contribute to tissue anoxia. Himwich has postulated a more important mechanism by which excessive tensions of oxygen might bring about histotoxic anoxia by a change in the nature of the protein moiety of the enzyme involved in the oxidation of pyruvic acid (pyruvic oxidase):

> This protein has sulfhydryl (SH) groups, and for the function of that respiratory enzyme the sulfhydryl groups must be kept intact. If in the presence of a high oxygen tension the hydrogen is oxidized away from the sulphur, the protein can no longer act in its capacity to facilitate the oxidation of pyruvic acid. Thus with poisonous concentrations of oxygen, glucose oxidation ceases at the pyruvic acid level and a condition of cellular or histotoxic anoxia is produced.

It is common knowledge that chemical and physiologic processes vary with temperature, which in turn is influenced by relative humidity. The premature infant inside the incubator is definitely acted on by both factors, but how much they determine growth and development of differentiating tissues remains to be investigated.

The Premature Host

Vascularization of the Retina

Terry's[15] hypothesis that RLF is due to a lack of involution of the hyaloid artery was discarded when Owens and Owens[11] reported onset after regression of that vessel and in previously clear fundi. Reese and Payne[17] emphasized the frequent association of RLF with cutaneous hemangiomas, the implication being that the biologic process involved tissues other than the eye, and suggested that RLF is determined by the developmental status of the primary vitreous.

The retina of the fetus during the last trimester of pregnancy is undergoing rapid vascularization. This developmental fact was demonstrated about the turn of the century by Versari[3] in Italy (Fig. 1) and recently confirmed ophthalmoscopically in the prematurely born infant by Fletcher.[4] About the fifth month of gestation the primordial vessels of the retina appear as vascular sprouts of the hyaloid artery radiating from the optic disk. Involution of the distal portion of the hyaloid artery traversing the vitreous gradually follows, and further differentiation of retinal vessels proceeds through the eighth month of intrauterine life in the usual course of events — or in an incubator if the infant is prematurely born.

Michaelson[5] made a further contribution to the understanding of retinal vascular morphogenesis in the kitten, rat and man by studies of India-ink-injected specimens of the developing retina. He demonstrated that as the hyaloid artery involutes to the level of its emergence from the optic disk, its persisting branches become the major retinal vessels. They generally consist of three sets of arteries and accompanying veins, which run from the optic disk toward the periphery of the retina, one pair nasally, one pair diagonally upward and out and one diagonally downward and out. A system of arteriovenous loops or arcades is made up of the main trunks composing this vascular tree, whose branches gradually extend farther and farther toward the periphery of the fundus. The capillaries develop from the venules of the arcades by endothelial extensions toward and almost as far as arteriolar blood vessels, which are left with a well marked capillary-free space around them. This zone is traversed, however, at scattered points by arterioles, which subdivide into glomerular-like capillaries and ultimately complete junction with newly formed endothelial extensions from the venules.

The fact that the capillary system of the retina is derived from the endothelium of the veins rather than of arteries, and the presence of a capillary-free zone around the arterioles led to the study of the various influences on the development of the vascular system in this area. The vascular anatomic peculiarities and physiologic behavior of endothelium indicated a substance that affects the growth of the vessels and is present in the extravascular tissue of the retina in a gradient of concentration varying between one extreme in areas traversed by arterioles and another extreme in regions traversed by venules; this substance is interpreted by F. W. Campbell[48] as oxygen.

With the hypothesis that a variable oxygen concentration in retinal tissue influences the development of blood vessels, Campbell found that capillaries proliferated actively when newborn rats were subjected to lowered oxygen tensions (Fig. 2). Conversely, with increased oxygen concentrations, there was a reduction in vascularization of the retina. Oxygen tension

not only determines morphogenesis of retinal vessels but also profoundly influences their function. Caliber, for example, varies promptly in response to oxygen content of the atmosphere both in the newborn[49] and in the adult fundus.[50]

Environmental Determinants of RLF

RLF, like the automobile accident, is an example of a condition that has appeared in almost epidemic proportions in recent years as a new disease and in relation to certain features of the socioeconomic environment. Since the turn of the century medical capacity for successful protection and rearing of prematurely born and partially developed infants has been extended farther and farther back toward their conception. This period has seen the perfection of artificial feeding, parenteral fluids, antibiotics, the premature nursery and the development of the modern incubator in which temperature and humidity are regulated and oxygen supplied in desired concentrations. The very intricacy and perfection of such a piece of apparatus — like that of an anesthesia machine capable of delivering measured amounts of cyclopropane gas — is accompanied with undefined hazards if things go wrong, whether they are sudden explosion, slow suffocation or more insidious disease arising because of unforeseen actions that go counter to normal homeostatic processes. The many environmental factors that bear on the purchase, place and operation of incubators are left unanalyzed; they surely influence the epidemiology of RLF and account for hitherto baffling distributions of the disease in the best equipped hospitals while smaller units and economically less favored areas were often spared.[36, 38, 51]

Szewczyk[36] has described some of the difficulties to be encountered during continuous operation of incubators that should be controlled in the future. A basic problem is to define the internal physiologic features of the prematurely born baby that determine interaction with various atmospheres and temperatures encountered in the modern incubator. The importance of defining whether the ocular lesion is due to tissue hyperoxia or tissue anoxia is at least twofold: because it is anticipated that a primary anoxic form may go overlooked, or at least unreported, as the incubator-induced disease comes under control and because an improved understanding of RLF will expectedly contribute to the understanding of the genesis of congenital anomalies.[52] In addition the control of body temperature, electrolyte constitution and antioxidant medication needs further attention.

Figure 2. *Retinal Vascular System in Young Rats (after F. W. Campbell[48]). Left=a six-day-old normal rat. Right=a nine-day-old rat after eight days at a simulated altitude of 17,000 feet. A=artery; V=vein.*

Physiologic Response in Atmospheres of Varying Oxygen Content

It is now clear that similar if not identical ocular pathology may be induced experimentally by antithetical disturbances of oxygenation — excessive oxygen at one extreme and anoxia at the other. To demonstrate the point, however, is not to explain the sequence of events set in motion when the infant or the laboratory animal is exposed to extreme concentrations of oxygen. Before conflicting aspects of the

problem can be harmonized pertinent investigations in physiology and biochemistry must be considered.

By ophthalmoscopic examinations of young adults studied under conditions of high and low oxygen supply in a pressure chamber Cusick and his associates,[50] in 1940, showed vasodilatation of arteries and veins at simulated high altitudes and marked diminution in caliber of retinal vessels when high concentrations of oxygen were breathed. These observations, made in young adult human beings, were confirmed in 130 prematurely born infants by Huggert[49] through weekly ophthalmoscopic examinations. Retinal vessels were often greatly narrowed during the administration of oxygen, and vascular dilatation and peripheral edema occurred in many cases when oxygen was stopped. In another study conducted on prematurely born infants, direct correlation existed between the inspired air and oxygen reaching the tissues; the arterial oxygen tension remained much higher than the tension in inspired air.[53] A content of 70 to 79 per cent of oxygen in the tent saturated the arterial blood, and lesser concentrations very nearly did so, showing that the levels of oxygen in the incubator are reflected and even exaggerated in the arterial blood supply and the tissues. If such high concentrations are maintained steadily during the first days of life of a newborn infant acclimatization to these high levels presumably takes place. What changes occur in an acclimated subject on abrupt exposure to lower levels of oxygen — the 20 per cent concentration of room air at sea level — is a crucial question for which there are some indications in the vascular congestion of the fundus observed after such transitions by Szewczyk[35] and Jefferson[38] and in the experiments of J. A. Campbell.[47]

Campbell subjected a rabbit to an atmosphere containing 40 per cent (290 mm. of mercury) of oxygen for twenty days, which was then increased to 60 per cent (416 mm.) for eighteen days more. When this animal was taken out of the chamber and exposed to normal atmospheric conditions, it appeared as handicapped in its endeavors to obtain oxygen from normal air as a normal animal abruptly exposed to an atmosphere with oxygen lowered to 85 mm.:

> The exposure to high O_2-pressure in the air lasted in all for 38 days; interesting after-effects were observed as the result of sudden return to normal O_2-pressure in the air again, revealing that the animal was unacclimatised now for normal pressure. The first effect noticed was hyperpnoea; total ventilation of the lung was not recorded accurately, but observation of the rate of breathing (30 p. c. increase) and of the movements of the chest and abdomen indicated definite hyperpnoea.

At this time the carbon dioxide tensions in the tissues were markedly decreased, and remained low for over two weeks, when the oxygen tension in the tissues had fallen from 53 to 32 mm. (a 40 per cent drop) whereas that under the skin had declined from 35 to 25 mm., the normal figures being 43 and 32 respectively.

Campbell also observed that after prolonged exposure to increased oxygen tensions hemoglobin and red-cell counts were considerably decreased and concluded that marked aftereffects connected with acclimatization were produced:

> Decrease of Hb and of red cells is an important factor in the later stages of acclimatisation to increased O_2-pressure in the air. The Hb fell from 85 to 55 p.c. and the red cells from 6.0 to 3.0 millions per c. mm.; the animals exhibited hyperpnoea and a marked fall of CO_2-tensions in the tissues — indicating O_2-deficiency — on reducing the O_2-pressure . . . to normal again.

Workers in the field of brain metabolism have observed the extraordinary tolerance to anoxia of the mammalian newborn as compared with the adult animal.[54] The difference is in the capacity of the immature brain to survive for relatively long periods without oxygen by obtaining energy anaerobically through glycolysis. Himwich[7] has shown that both

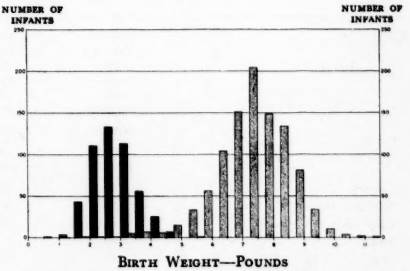

FIGURE 3. *Distribution of Cases of Retrolental Fibroplasia (Black) in Relation to Birth Weights of 1000 Babies in a General Population (Gray).*

anaerobic and aerobic types of metabolism rise as growth proceeds but that oxygen consumption, an indication of aerobic metabolism, soon outstrips anaerobic glycolysis. This shift from the anaerobic to the aerobic derivation of cerebral energy is found to be the result of enzymatic changes, mainly owing to the appearance of new enzyme systems and also to increased concentrations of enzymes already present. Biochemical conditions similar to these in the central nervous system may well come into play in the retina, an area that, ontogenetically, is part of the brain.

Enzyme activity and cellular metabolism are known to be accelerated by increases of temperature; Miller et al.[55] have questioned the wisdom of maintaining asphyxiated infants in incubators held at body temperatures that are supposedly optimal. His experiments with newborn guinea pigs and rabbits point to the fact that undue warmth is detrimental to survival of anoxic newborn animals. Likewise, the generally accepted practice of keeping the markedly premature infant at relatively high temperatures may influence systemic and local reactions to oxygen supply.

Epidemiology

The first striking characteristic of the mass disease to be established was statistical confirmation of Terry's clinical observation that RLF is generally restricted to infants whose birth weights correspond with those of fetuses of the last trimester of pregnancy — around 3.0±.5 lb. or 1300±200 gm. (Fig. 3). The implications of a host factor (the fetal retina) are definite. In some hospitals RLF has developed in as many as 20 or 30 per cent of this group of infants in recent years.

Although RLF has unfortunately (in the interest of a quicker solution of its epidemiology) never been reportable, there is solid evidence that it has been much more frequently encountered around the world in the past ten years, particularly in the postwar period.[19] Kinsey and Zacharias,[21] in a survey in the United States in 1949, observed a significant rise in incidence after 1942 that could not be explained by the assumption that the disease was formerly unrecognized or that a significantly greater proportion of premature infants now survive for the condition to develop. About half the number of recognized cases occurred in New York, Chicago, Boston and Baltimore; in some large cities like Los Angeles and San Francisco the disease was rarely seen. The indications are that a great variation in the geographic distribution of the disease has existed in different areas of the same country and even in different centers within the same city.

The only figures available thus far on a community basis are those accumulated by the National Society for the Prevention of Blindness. From study of 2796 cases of blindness in persons under twenty-one years of age in seven states, it was estimated that the average annual incidence of blindness per 100,000 of the population under that age was around 1.5 for many years before 1935. Thereafter, with improved control of many infections leading to blindness, the rate dropped (Table 1) until 1941-1945. In 1946-1950, RLF accounted for a third of all blindness in persons under twenty-one years of age. Whereas rates of blindness from all other causes have been steadily declining during the past decade loss of vision as a result of RLF has increased considerably. More recent studies indicate that 75 per cent of new cases of blindness are coming from the part of the population under one year of age — in other words, most new cases are caused by RLF (Table 2).

For a while it appeared as though RLF were confined to the United States, but search for the condition in other parts of the world eventually revealed its presence first in Vancouver[56] and then in Montreal, Canada.[57] The first British accounts of the disease, which appeared in 1949,[58] were followed by reports of its occurrence in almost epidemic proportions in 1950-1951.[38,59] In Sweden Bjelkhagen[60] and Lindblad[61] discovered 38 cases of RLF in infants of birth weight of 2200 gm. or less born from 1945 to 1950.

Table 1. *Trends in Incidence of Blindness in Children, by Cause.**

Cause	Average Yearly Rate Among 544 Children 1926-'30 *per 100,000*	Average Yearly Rate Among 552 Children 1931-'35 *per 100,000*	Average Yearly Rate Among 490 Children 1936-'40 *per 100,000*	Average Yearly Rate Among 529 Children 1941-'45 *per 100,000*	Average Yearly Rate Among 681 Children 1946-'50 *per 100,000*
All causes	*1.50*	*1.57*	*1.44*	*1.48*	*1.83*
Infectious diseases	0.33	0.26	0.14	0.14	0.09
Ophthalmia neonatorum	0.09	0.05	0.02	0.02	0.01
Syphilis	0.10	0.07	0.05	0.04	0.02
Other	0.14	0.14	0.07	0.08	0.06
Injury	0.13	0.12	0.10	0.10	0.09
Poisonings	—	<0.01	0.01	—	<0.01
Tumors	0.03	0.06	0.07	0.07	0.09
General diseases	0.03	0.03	0.02	0.02	0.02
Prenatal influence	0.81	0.82	0.91	0.99	1.37
Retrolental fibroplasia	—	—	0.04	0.29	0.81
All other prenatal conditions	0.81	0.82	0.87	0.70	0.56
Etiology undetermined	0.17	0.28	0.19	0.16	0.17

*Based on *Trends of Blindness in Children*. National Society for the Prevention of Blindness exhibit at annual meeting of American Academy of Ophthalmology and Otolaryngology, Chicago, October 11-16, 1953.

Lelong and his associates[33] examined the eye-grounds of all prematurely born infants in the École de Puériculture, Paris, between February, 1950, and February, 1951, and detected 11 cases of RLF among 146 infants weighing 1800 gm. or less at birth. They extended Ingalls's concern with hypoxia to hyperoxia (suroxygenation) and concluded that for better understanding of the process it would be necessary to define, meticulously, conditions of oxygen supply. A new and as yet unformulated hypothesis was emerging: that the newest incubators with their capacity for delivering oxygen in almost pure concentration could be regarded as the primary inciting cause of the postwar "epidemic" of RLF. For analysis of pertinent clinical, laboratory and epidemiologic investigation it is necessary to bear in mind considerations of oxygen dosage and adaptation as well as anoxic, anemic, stagnant and histotoxic anoxia. Some of these variables had already been fortuitously changed as new incubators were introduced into some premature nurseries but not others.

In December, 1950, K. Campbell[34] reported on premature infants nursed in different institutions in Australia under similar environmental conditions except for the amount of oxygen breathed. One group, comprising 123 infants, were exposed to oxygen in cots, introduced in 1948, capable of delivering oxygen in 40 to 60 per cent concentrations; RLF developed in 23. Another group of 58 were given oxygen sparingly — by nasal catheter or rarely by tent or cot; RLF occurred in 4. In 1950, when the use of oxygen was drastically reduced, no more cases of RLF appeared that year nor among the next 30 premature babies delivered in 1951.

TABLE 2. *Cases of Blindness Occurring in 1946-50, by Age at Onset of Blindness.**

AGE AT ONSET	PERCENTAGE OF TOTAL†	YEARLY RATE
		per 100,000
Under 1 yr.	75.3	22.00
1 to 6, inclusive	12.2	0.63
7 to 20, inclusive	8.8	0.27
Exact age unknown	3.7	—
Under 21	100.0	1.83

*Based on *Trends of Blindness in Children*. National Society for the Prevention of Blindness exhibit at annual meeting of American Academy of Ophthalmology and Otolaryngology, Chicago, October 11-16, 1953.
†681 in this group.

In 1952 Crosse[59] and Crosse and Evans[62] reviewed experience with prematurely born babies in Birmingham, England. There had been practically no cases of RLF in that city until 1948, when, as in Melbourne, new units with facilities for high oxygen administration were established; coincidentally a significant rise in yearly incidence of RLF occurred. The practice of liberal administration of oxygen was abandoned in 1951, and no new cases were observed in 1952.

Shortly thereafter Jefferson[38] witnessed the most dramatic outbreak of RLF yet to be reported — in Manchester, England. She studied 629 surviving infants nursed in premature units and found a sharp increase in incidence of the disease in 1950 and 1951; only 3 cases had been recognized before 1950. The change in incidence of RLF was closely linked with changes in the method of administration of oxygen (Fig. 4). Before 1950 oxygen had been given by face-mask when indicated, and only rarely had infants been placed in high tensions of oxygen. However, the following events occurred when the technic was changed:

In December, 1949, oxygen tents were introduced on the unit and were used routinely for all infants under 3 lb.; in the following months three cases of retrolental fibroplasia occurred in this weight group. In November, 1950, it was decided to nurse *every* infant on the unit naked in an oxygen tent. Following this, infants whose birth weight was over 3 lb. began to develop the disease. The next change came in March, 1951, when soft plastic covers were introduced for use on the Sorrento-type cot.

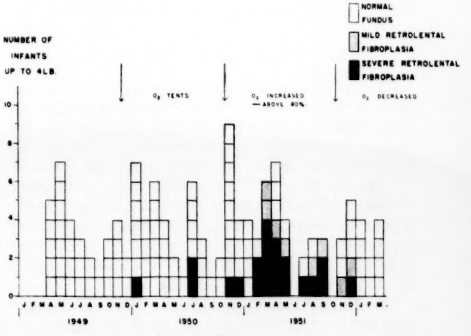
NORMAL FUNDUS
MILD RETROLENTAL FIBROPLASIA
SEVERE RETROLENTAL FIBROPLASIA
NUMBER OF INFANTS UP TO 4 LB.
O2 TENTS
O2 INCREASED — ABOVE 80%
O2 DECREASED
0
2
4
6
8
10
J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M.
1949
1950
1951
TIME IN MONTHS

FIGURE 4. *Incidence of Retrolental Fibroplasia in Relation to Method of Oxygen Administration, in Premature Infants at St. Mary's Hospital, Manchester, England, 1949-52 (Based on Jefferson[38]).*
Black represents severe RLF, gray mild RLF, and white no ocular disease.

These made it possible to maintain the infants' temperature without using a tent and resulted in the infants being removed earlier from high tensions of oxygen. Almost synchronous with this change there was a further increase in number of affected infants of birth weight up to and including 4 lb.; about 75% of the infants in this weight group showed evidence of the disease during this period. It was later discovered that an atmosphere of 80-85% oxygen developed within the tents when the oxygen flow was 2 litres/min.; when the flow was reduced to 0.5 litres/min., which was the minimum rate possible with the apparatus, there was still 60% oxygen inside the tents. Therefore the infants on removal from the tents had been subjected to a sudden reduction in the percentage of oxygen they were breathing of from 60% to 20%. In October, 1951, the use of oxygen was reduced to a minimum and its withdrawal was carefully graded. Since that time only one serious case and two relatively mild cases of retrolental fibroplasia have occurred.

These changes in technic and apparatus were accidental, but a review of the sequence of events reveals a clear demonstration of the appearance of severe RLF after premature infants were subjected to high tensions of oxygen in modern incubators. Results indicate decisively that all present attempts to study premature infants under prolonged high oxygen concentrations should be terminated; the facts are too clear-cut to warrant the risk of further injury.

There is a suggestion in the experience described above that thermal factors have played an accessory role in the ocular disease because the plastic covers made it possible to maintain the infants' temperatures without the use of a tent. Moreover, the fact that an outbreak of RLF developed abruptly even though infants were being removed earlier from high tensions of oxygen argues in the same direction. We believe that this factor of temperature needs scrutiny especially since it is a fairly universal practice to keep premature infants at adult body temperatures. This part of the problem can be clarified by planned experiments with animals in the laboratory.

Control Program

Clinical and epidemiologic observations in many parts of the world confirm the hypothesis that excessively high concentrations of oxygen may initiate abnormal development of the vascular system of the premature retina and ultimately result in blindness — and doubtless still undetermined effects on other tissues of the body. Exactly how this is brought about is yet to be ascertained by suitably planned laboratory experiments. That a useful therapeutic agent may have toxic limitations has parallels in many branches of therapeutics and preventive medicine.

In Birmingham, England, the epidemic incidence of RLF has been abolished by restriction of the administration of oxygen to patients showing cyanosis and limitation of the percentage of oxygen to the minimum required to keep the infant pink. Crosse[63] points out:

> Since the adoption of this practice, the survival rates have been maintained at the same level, but no further case of blindness has occurred. Two cases with early reversible changes occurred in one of the Units: they both returned to normal without treatment, and would not have been recognised if a routine weekly ophthalmic examination had not been carried out. It was interesting to note that both these cases required considerably larger amounts of oxygen than usual for their survival.

This observation of 2 premature infants with reversible changes in the fundi despite the graded use of oxygen is compatible with reports by Krause[16] and Szewczyk[64] of RLF in infants born at term, by Jefferson[38] of RLF in an infant never subjected to oxygen therapy and by Reese et al.[65] of dilated retinal vessels, multiple hemorrhages and edema of the retina in an infant on admission to the premature nursery during the neonatal period. It seems probable that a hypoxic, sporadic form of RLF will be uncovered as the incubator-induced epidemic subsides. Certainly, the five structural sequences of RLF described by Reese, King and Owens[65] correspond with minute precision to those expected from hypoxia of the retina; moreover, similar structural changes have been induced by hypoxia in the mouse fetus.[37] The inference is drawn that hyperoxia induces its structural changes through a series of events leading to histotoxic anoxia of the retina. If other factors such as body heat and systemic hypoxia influence onset and development of RLF this kind of disease will emerge as an epidemiologic entity as the incubator-induced form subsides. In the interests of obtaining further information on these points effort should be made to strengthen reporting of RLF.

Summary and Conclusions

Retrolental fibroplasia is the end stage of retinal vascular malformation brought on most frequently in the prematurely born infant by excesses of oxygen supply in the neonatal period of life. Other factors such as excessive warmth and humidity, electrolyte shifts, antioxidants and enzyme derangements probably influence onset and severity of the condition. These factors limit survival, and may determine ocular or other disease in the immature fetus. The mechanism by which retrolental fibroplasia develops in high oxygen is postulated as histotoxic anoxia brought on by derangement of tissue enzymes at critical periods of fetal development.

Clinical, experimental and epidemiologic evidence is reviewed to show that the anomaly of the retinal vascular system has been prevented by careful attention to optimal supply of oxygen. As the incubator-induced form of the disease is brought under control it seems likely that a more intractable, sporadic form will emerge that is brought on by a concatenation of circumstances involving repeated or prolonged bouts of anoxia and some of the factors listed above.

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CLAMPING OF THE UMBILICAL CORD*

Its Effect on the Placental Transfusion

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IT is difficult to assay the various methods of umbilical-cord clamping. Every physician employs a different technic and usually establishes a pattern that he carries out routinely in his obstetric work. At times this pattern is influenced by the equipment, the nursing situation, hospital policy in care of the newborn and various emergencies arising in the mother or the infant. Thus, in some cases, the infant is placed on the mother's abdomen while the physician attends to a bleeding episiotomy, or on a small delivery table beneath the level of the mother, with consequent delay in cord clamping. It has been observed that the cord is often clamped immediately, either as a routine procedure or so that the infant can be handed to a nurse for resuscitation and aspiration. At times, and because of recently renewed interest in the subject,

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the cord is methodically stripped before clamping. This study concerns the various methods of interrupting the fetal-placental circulation.

Physiologic Review

In the process of development the fetus is in an environment of relatively high oxygen concentration, which gradually becomes one of anoxemia as term is approached. As the period of gestation advances the hemoglobin and number of erythrocytes increase. At birth the respective values are approximately 17.6 gm. per 100 cc. and 5,100,000.[1] According to DeMarsh, Alt and Windle[2] the blood volume of the newborn infant exclusive of the placenta averages about 313 cc. Most of the figures for the amount of blood available in the placenta were arrived at in the process of experimental work on umbilical-cord blood. It must be borne in mind that not all the blood in the placenta is retrievable. Windle[3] reports an average of 108 cc. Another average reported is 70 cc. In an experiment at Cahill House, Cambridge City Hospital, in which approximately 500 samples of cord blood were drawn, the average volume was 75 to 80 cc. From these figures, it can be concluded that approximately a fourth of the fetal-placental blood volume remains in the placenta. With 10 cc. of blood per 300 gm. of body weight as the accepted criterion for transfusion in an infant the placental blood would at least represent an adequate transfusion for a 3000-gm. infant.

At birth one of the most important physiologic phenomena in the infant is the deprivation of oxygen. As stated above, there is an increasing degree of anoxemia as term is approached. According to Reynolds[4] this depends on the source of the corpuscles. Thus, in early pregnancy, when connective-tissue elements are the source of the cells, the oxygen-carrying capacity is low, rising to a high level in the middle of pregnancy, when the fetal liver is the source. Toward the end of gestation, the source is the adult type of bone marrow, whose cells are relatively poor in their ability to carry oxygen. Occlusion of the umbilical cord at this point further increases the degree of anoxemia. The infant draws in its first gasps of air and is thus transferred from its maternal supply of oxygen to that of the atmosphere. The oxygen-carrying capacity of the erythrocytes, which at this point assumes greatest importance, is diminished. To offset this there must be an increased number of red blood cells. The erythrocyte count of the fetus is at its maximum at birth. But this increase must be reflected in the fetal blood stream, and not that which is left as part of the inert placental pool.

General Considerations

The value of getting as many corpuscles as possible into the fetal circulation becomes immediately apparent from a purely physiologic point of view. In addition the general welfare of these infants is improved in the immediate neonatal period.[5] No one can deny the salutary effects of blood and its importance in bodily nourishment, metabolism and growth, especially when one is dealing with the premature infant. These factors are of equal and perhaps greater importance in infants delivered after such bleeding accidents as placenta praevia, abruptio placenta, marginal separation and vasa praevia, as well as those who have undergone a traumatic delivery and those born by cesarean section. All these situations cause severe shock and additional blood may greatly increase the possibility of survival.

This leads to the question of exposing the infant to the placental transfusion by various technics such as delayed cord clamping or cord stripping, or both.

In 1950 McCausland et al.[6] conducted a survey among 1900 diplomates of the American Board of Obstetrics and Gynecology revealing that approximately two thirds regarded the matter as of minor importance. It is interesting, however, that of this total number 455 used the stripping procedure.

The effect of blood loss to the infant coincident to rapid clamping of the cord, common in cesarean section, is brought out by the study of Landau and his associates.[7] In investigating fetal mortality after cesarean section, these authors described babies in whom symptoms, consisting of cyanosis, respiratory distress, air hunger, costal retraction, and rapid, weak pulse, developed two to four hours after birth. Death, which was attributed to hematogenic shock, occurred less than twenty-four hours later. The authors considered the fatal shock to be due to blood deprivation after immediate cord clamping. In a series of 87 cases in which the placenta was held above the infant so that the blood drained into it none of the infants manifested this shock-like state.

In 100 unselected infants delivered by cesarean section, Siddall, Crissey and Knapp[8] employed immediate clamping in 50 cases and stripping in the other half. The average hemoglobin and red-cell count were 15.9 gm. per 100 cc. and 4,760,000 for the former and 17.2 gm. per 100 cc. and 5,350,000 for the latter. The former also showed a 16.7 per cent, and the latter a 26.1 per cent increase over birth weight at discharge.

The problem of whether delayed clamping or stripping is more efficacious is discussed by McCausland and his associates,[6] who believe that stripping accomplishes more. The arteries stop pulsating shortly after delivery,[3] so that only the vein remains distended, through which blood is forced into the fetus with each uterine contraction. Reynolds[9] states that one can make the blood from the placenta pour through the umbilical vein back into the infant simply by lowering it below the level of the placenta.

No reports of ill effects are found in the literature. There are numerous references to the possibility of

icterus, but this did not occur in the series of McCausland, Holmes and Schumann,[6,10] and no cases of icterus have been reported by any investigators.

An editorial comment on this work[10] considered delayed ligation desirable but feared that stripping might carry some danger of expressing tissue juices or particles into the blood stream. An editorial note on the article published in 1950[6] stated that the recommendations for cord stripping could be accepted as safe and also that the long disregard of cord stripping has been a regrettable lapse in technic.

Material and Methods

The infants in this series were delivered by the house staff under my supervision or that of another resident. All the mothers had been regular attendants of the prenatal clinic and had been put on the routine iron regimen. The socio-economic status of the patients attending the clinic, however, prohibits any accuracy in determining their dietary habits and their regularity of medication. Since adequate prenatal nutrition is extremely important and is reflected in the general condition of the newborn, it is immediately apparent that this unavoidable lack of supervision could account for some variation in an experiment such as this one.

Four different technics were utilized in clamping the cord. These were the most common methods used by a majority of operators.

Group 1

The infant was placed on the mother's abdomen (above the level of the placenta), and the cord was clamped after the arteries had stopped pulsating and the vein no longer filled.

Group 2

The cord was clamped immediately after delivery.

Group 3

The infant was placed on a table (below the level of the placenta), and the cord was slowly and methodically stripped from the vulva to the umbilicus. When the cord was no longer distended with blood, it was clamped. Four to eight strippings were usually necessary.

Group 4

The infant was placed on a table (below the level of the placenta), and the cord was clamped when all pulsations and distention had ceased.

Infants from Rh-mothers, regardless of titers, were not included in this series, principally to keep the series as homogeneous as possible and to avoid the introduction of antibodies, whether or not previously detected in the maternal circulation. Premature infants and those born after hemorrhagic episodes before and during birth, as well as those delivered by cesarean section, were also excluded. Infants showing any abnormality or infection were dropped from the study. Cases of midforceps, rotation and breech delivery or in which any traumatic factors were involved were omitted. Only those delivered without incident were included.

Analgesia consisted mainly of Nembutal and Demerol or Nisentil given in moderate doses. Saddle block, nitrous oxide, oxygen and ether and pudendal block were the three methods used for anesthesia. Saddle block was usually employed for primiparas, and nitrous oxide, oxygen and ether for multiparas. Patients who had recently eaten received pudendal or saddle block.

Blood was obtained from the infants by heel puncture approximately twenty-four hours and again seventy-two hours after birth. To reduce human error to a minimum, I drew all the blood samples, and the determinations were all done by the chief technician or under her supervision. Standard blood pipettes were used. The Haden–Hausser method was employed to determine the hemoglobin values.

One hundred consecutive unselected cases (except as noted above) were included. Thus, each group consisted of 25 cases. The laboratory was never aware of which technic of cord clamping was being utilized at the time of its determinations.

Results

The results in the various groups are shown in Table 1. It is immediately apparent that the best hematologic response resulted from Group 3 (cord stripping) and the poorest from Group 2 (immediate clamping). Some of the individual red-cell and hemo-

Table 1. *Effect of Umbilical-Cord Clamping and Stripping on Red-Cell and Hemoglobin Values.*

		Red-Cell Count				Hemoglobin			
Group	No. of Cases	Range	Average after 24 hr.	Average after 72 hr.	Average total	Range	Average after 24 hr.	Average after 72 hr.	Average total
		x10⁶	*x10⁶*	*x10⁶*	*x10⁶*	*gm./100 cc.*	*gm./100 cc.*	*gm./100 cc.*	*gm./100 cc.*
1	25	4.65-6.40	5.71	5.82	5.77	15.0-19.0	17.38	17.08	17.19
2	25	3.99-5.50	4.74	4.78	4.76	12.0-17.0	14.85	14.71	14.78
3	25	5.60-7.10	6.46	6.47	6.47	16.5-20.0	18.62	18.96	18.79
4	25	4.50-6.50	5.80	5.80	5.80	15.5-19.0	17.50	17.30	17.15

globin values were extremely low: red-cell counts of 3,990,000 and hemoglobin levels of 12 gm. per 100 cc. are not to be taken lightly, even in a normal newborn infant.

The good results obtained in Group 1 were somewhat surprising, since holding the infant above the level of the placenta was thought to deprive it of blood. However, the uterine contractions obviously play a major role in forcing blood through the umbilical vein.[3]

Group 4 compares favorably with Group 1, since the same mechanism is probably in effect along with some help from gravity, as stated by Reynolds.[4]

Although an attempt was made to evaluate the respective weights and general condition in the immediate neonatal period, no definite conclusions could be made. The infants are usually discharged on the fifth day, and no startling differences in weight could be established. As a matter of fact, in this short time, most of the babies did not regain their original birth weights, and differences in cord-clamping technic did not appear to influence weight gain or loss. No particular differences in general well-being were noted. However, it must be borne in mind that these were all normal infants born of mothers with no obstetric complications. Therefore, it is conceivable that such an infant can tolerate a mild anemia without any deleterious effects.

The primary purpose of this paper is to illustrate that varying technics of cord clamping can influence an infant's blood picture. Thus, when one is confronted with a situation that produces shock, a method of clamping the cord should be utilized that will offer the infant the maximum benefit of its placental transfusion. Cord stripping appears to have that effect.

Too often, after a traumatic delivery or intrapartum bleeding episode, the physician is in great haste to clamp the cord and give a pale, listless infant to a nurse for aspiration and resuscitation. Usually, these infants are described as having asphyxia pallida, and their prognosis is grave. They respond poorly to oxygen administration, and worse to other heroic measures of resuscitation. Their main difficulty is shock and blood loss, which are inadequately corrected by oxygen and are not improved by rough handling. I have seen several infants with asphyxia pallida (not included in this series, of course) who were very pale and listless, with a rapid pulse and a very weak cry; with gentle, slow, methodical cord stripping, they were transformed within a few minutes to ruddy, lustily-crying infants. Suction and oxygen administration were then resorted to secondarily. The prognosis immediately improved.

Another situation commonly encountered is the infant with a loop or two of cord around its neck. Usually, the most expeditious measure is to clamp and cut the cord in situ. This actually amounts to immediate clamping in an already depressed baby. Every effort within reason should be made to slip the loops over the infant's head and allow it the benefit of its own blood.

Summary and Conclusions

The fetal-placental circulatory physiology is briefly reviewed.

A study of four technics of cord clamping and their effect on the blood of 100 normally delivered infants is presented. Cord stripping is considered the most efficacious method of improving the infant's blood picture, with delayed clamping next in preference. Immediate clamping, by far the worst method, deprives the infant of blood.

Cord clamping apparently has no influence on the weight or general well-being of the normal infant delivered without obstetric complications. Such an infant can adjust itself adequately to a moderate anemia. Conversely, it is apparently no better off, at least clinically, with an increased amount of blood.

Cord stripping or delayed cord clamping or both are urged to effect a maximum placental transfusion in infants who are shocked after a traumatic delivery, anemic after a bleeding accident before or during birth, delivered by cesarean section or born prematurely.

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DIABETES INSIPIDUS ASSOCIATED WITH EDEMA*

Report of a Case, with Discussion of the Physiologic Implications

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DIABETES insipidus, a syndrome characterized by polyuria, polydipsia and excretion of urine of low specific gravity, may result from a deficiency of the neurohypophyseal antidiuretic hormone.[1] Since this hormone is presumed to control the "facultative" reabsorption of water in the distal tubule of the kidney the specific physiologic "defect" in diabetes insipidus is usually attributed to a decrease or absence of renal reabsorption of water in this portion of the nephron.[2] As a consequence of this physiologic abnormality, the untreated patient with diabetes insipidus may suffer from dehydration resulting from loss of water in excess of intake, unless he is able to restore and maintain the body water balance by the ingestion of sufficient fluid.

Because the tendency to a negative water balance characterizes this disease, it is of particular interest to report a case of diabetes insipidus (secondary to metastatic neoplastic invasion and destruction of the posterior lobe of the pituitary gland) in which massive edema of the lower extremities occurred during the course of the disease, and in which pulmonary edema also developed during the intravenous administration of hypertonic saline solution (Hickey–Hare test for diabetes insipidus). This case thus poses interesting physiologic questions concerning the role of the antidiuretic hormone in the formation of edema.[3,4]

Specific abnormalities of electrolyte metabolism have not been definitely established either for the clinical disease of diabetes insipidus or for the syndrome produced experimentally in animals. However, in contrast to the usual picture, this patient demonstrated both persistent sodium retention and hypokalemia.

The aims of this communication are first, to describe the course of a patient suffering from diabetes insipidus associated with abnormalities of water and electrolyte metabolism hitherto unreported and, secondly, to discuss the physiologic implications of this clinical picture.

CASE REPORT

P.V. (M.S.H. No. 715), a 58-year-old Greek man, approximately 1½ months before admission to the hospital on November 8, 1952, noted a mild, continuous "pressing" pain over the right side of the head that subsided spontaneously 1 week before admission. One week after the onset of the head pain, severe dryness of the mouth developed, causing him to drink "gallons" of fluid daily. During the 3 weeks before admission he lost weight (25 to 30 pounds), and a cough productive of small amounts of a slightly yellowish sputum, unaccompanied by hemoptysis, chills, fever, "night-sweats" or chest pain, developed; he complained of having felt an increased need for fresh air, and noted ankle swelling.

Physical examination showed a darkly pigmented, well developed, lethargic, dehydrated man. The neck veins were not distended. The lungs were resonant on percussion, with scattered rales and wheezes heard in both lung bases, and clearing on coughing. The heart had a regular rhythm. The 2d aortic sound was greater than the 1st, and a soft, Grade 1, apical systolic murmur was heard. The liver edge, which was hard and nontender, extended 2½ fingerbreadths below the right costal margin. The spleen was not palpable, and no ascites was detected. There was + pitting, sacral and bilateral pretibial edema. Both femoral pulses were palpable.

The temperature was 101.2°F., the pulse 88, and the respirations 24. The blood pressure was 140/72.

Examination of the blood revealed a hemoglobin of 14.9 gm. per 100 cc. and a white-cell count of 10,850, with 77 per cent neutrophils, 19 per cent lymphocytes and 4 per cent monocytes. The erythrocyte sedimentation rate was 17 mm. per hour. A random urine specimen had a specific gravity of 1.005, with a + test for albumin and no glucose; microscopical examination disclosed no red blood cells and 5 to 10 white blood cells per high-power field in the centrifuged urinary sediment. The blood urea nitrogen was 15 mg., glucose 140 mg., calcium 9.5 mg., phosphorus 3.6 mg., total protein 5.9 gm. (albumin 3.4 and globulin 2.5 gm.), bilirubin 0.4 mg., total cholesterol 238 mg., alkaline phosphatase 6 King–Armstrong units, creatinine 1.6 mg., and uric acid 3.5 mg. per 100 cc. The chloride was 104 milliequiv., carbon dioxide 36.1 milliequiv., sodium 164 milliequiv., and potassium 3.0 milliequiv. per liter. Bromsulfalein retention was 24 per cent. Cephalin flocculation was negative. The prothrombin time was 13 seconds (control, 13 seconds). The blood Wassermann reaction was negative. A phenolsulfonephthalein test showed 70 per cent excretion of the dye in 2 hours. A lumbar puncture on November 17 revealed an initial cerebrospinal-fluid pressure equivalent to 205 mm. of water, falling to 128 mm. after the withdrawal of 10 cc. of slightly opalescent fluid that contained 85 cells per cubic millimeter (but with the additon of acid only 8 cells per cubic millimeter, all mononuclear). The spinal-fluid Wassermann and colloidal-gold tests were negative; the protein was 47 mg., and the glucose 62 mg. per 100 cc., and the chloride 131 milliequiv. per liter.

An electrocardiogram on November 12 showed regular sinus rhythm, left-axis deviation, small Q and low T waves in Lead 1 and small Q wave in Lead aVL; in the multiple precordial leads the T wave was isoelectric in V_5. An electroencephalogram was normal. X-ray studies on the next day demonstrated a pulmonary soft-tissue density localized in the posterior part of the thorax. An intravenous urogram on a single film study revealed no distention of either urinary tract. Examination of the skull disclosed no abnormality.

By November 15 the ankle and leg edema had become massive, extending up above the knees. The venous pressure, measured in the arm, was equivalent to 4.5 cm. of water, rising to 5.5 cm. on pressure over the right upper quadrant of the abdomen. The circulation time (Decholin)

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was 18.5 seconds. Pressure in the left femoral vein on November 17 was equivalent to 5.5 cm. of water, excluding venous obstruction as a cause of the peripheral edema.

During the control period (November 11 to November 15) the 24-hour urinary excretions of sodium, chloride and potassium averaged 28, 45 and 61.5 milliequiv. respectively (Fig. 1). Since the patient was on a regular ward diet providing approximately 85 to 102 milliequiv. of sodium chloride per day, these urinary data suggested that he was

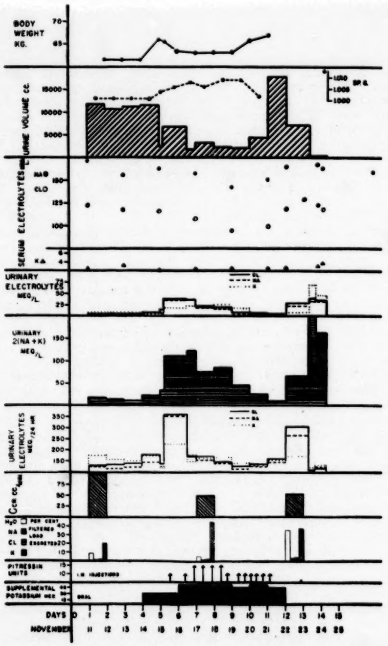

FIGURE 1. *Water and Electrolyte Metabolism, including the Effects of Pitressin Therapy, in a Patient with Diabetes Insipidus Associated with Edema of the Lower Extremities.*

retaining sodium chloride, the exact extent of the retention depending on the intake of food. Pitressin was discontinued on November 21, and in this 24-hour period he voided 17,830 cc. of urine containing 2.5, 3.4 and 3.3 milliequiv. per liter, respectively, of sodium, chloride and potassium. On the next morning the concentrations of sodium, chloride and potassium in the serum were 165, 119.4 and 2.7 milliequiv. per liter.

On the morning of November 22 the diuretic response to intravenous administration of glucose in 5 per cent water (flowing at 10 cc. per minute) and the antidiuretic response to single intravenous injections of Pitressin (0.57 units and 1.14 units per kilogram of body weight) were studied by methods previously described.[3,4] The results are presented in Figure 2. There was immediate attainment of peak diuresis in contrast to the time (85.1 ± 32.3 minutes) required normally under similar experimental conditions.[3] In addition there was a subnormal antidiuretic response to the single intravenous injections of 0.57 units and 1.14 units of Pitressin per kilogram of body weight. After the studies on intravenous hydration and Pitressin antidiuresis had been completed, with the patient's urine flowing at 21 cc. per minute, the intravenous administration of 2.5 per cent of sodium chloride (0.25 cc. per kilogram of body weight per minute) was begun.[5,6] For the next 2 collection periods (15 and 11 minutes each) the urine flow was 24.3 cc. and 20.9 cc. per minute respectively. Twenty-six minutes after the onset of the intravenous infusion of hypertonic saline solution pulmonary edema suddenly developed without any premonitory symptoms or signs. The infusion was discontinued immediately. The respiratory rate was 25 per minute, and the heart rate below 100 per minute, with a regular and full pulse. Oxygen by mask and 10 mg. of morphine sulfate (subcutaneously) were administered at once. During the next 2 hours the dyspnea and rales disappeared. An electrocardiogram taken soon after the onset of the pulmonary edema was indicative of coronary insufficiency, which subsided within a few hours.

At 1:00 a.m. on November 23 the respiratory rate was 28 per minute; the pulse was weak, and the heart sounds fair, at a regular rate of 160 per minute. By 7 a.m. the blood pressure had fallen to 60/40; the patient was unresponsive,

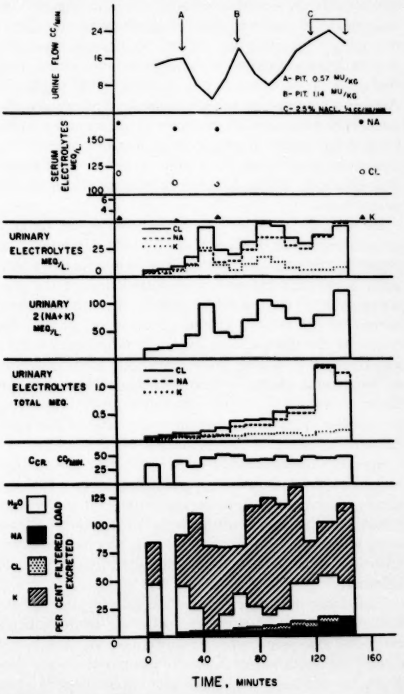

FIGURE 2. *Effects of Intravenous Injection of 5 per cent Glucose in Water, Pitressin and 2.5 per cent Sodium Chloride on Serum and Urinary Electrolytes.*

tachypneic (rate of 50 per minute) and appeared dehydrated. Rhonchi were heard at both bases. An electrocardiogram showed no definite evidence of an acute myocardial infarction. An intravenous infusion of 5 per cent glucose in water containing potassium chloride and Levophed was begun; 4000 cc. of urine had been passed since the previous morning, but only a small amount in the 7 hours since midnight. Pitressin, 15 units, was administered intramuscularly, and 450 cc. of clear urine was obtained by catheteri-

zation at 8:30 a.m. In the next 3½ hours the patient began to respond. The systolic blood pressure was maintained at 80 to 100 by means of intravenously administered Levophed. The respirations slowed to 30 per minute and became more regular. The concentrations of sodium and potassium in the serum were 167 and 2.0 milliequiv. per liter. Blood drawn at 8:00 p.m. yielded a sodium of 167 milliequiv., chloride of 123.4 milliequiv. and potassium of 3.1 milliequiv. per liter. By 9:00 p.m. the patient had received 3000 cc. of 5 per cent glucose in water, along with 7.5 gm. of potassium chloride and 6 cc. of Levophed. He had voided 900 cc. of urine during this period. The hematocrit was 46 per cent. The electrocardiogram gave no evidence of hypopotassemia, and further administration of potassium chloride was therefore discontinued. There was little change in the patient's condition during the night, and at 12:50 p.m. on November 24 he was found dead.

At autopsy the pertinent pathological findings included a primary bronchogenic carcinoma in the left hilar region, about the size of a tangerine, with infiltrations into the mucosa of the left lower bronchus and invasion of the hilar lymph nodes, which were enlarged. Microscopical examination showed the neoplasm to be an undifferentiated anaplastic carcinoma. There were metastatic nodules in the liver. The adrenal glands disclosed cortical hyperplasia, and metastatic infiltration of the medulla and cortex. A metastatic ulceration of the duodenal mucosa was noted. A tumor nodule, 4.3 by 3.0 by 4.0 cm., was found in the left frontal lobe of the cerebrum, and the posterior lobe of the pituitary gland was invaded and partially replaced by metastatic carcinoma. The heart was enlarged, weighing 330 gm., with thickening of the left ventricle. The left anterior descending and right coronary arteries showed sclerotic thickening, with plaque formation. The kidneys demonstrated some congestion, but there was no evidence of intrinsic renal disease.

The pathological findings indicated that in this patient the syndrome of diabetes insipidus resulted from destruction of the posterior lobe of the pituitary gland by metastatic carcinoma originating in the lung.

Edema

The formation of edema in this case may be considered under two major headings: fluid retention not resulting primarily from excessive retention of sodium ("nonsodium retaining"), and fluid retention secondary to that of sodium ("sodium-retaining").

"Nonsodium Retaining" Edema

Hypoalbuminemia. The concentration of serum albumin was 3.4 gm. per 100 cc.—high enough virtually to exclude hypoalbuminemia as a factor in the pathogenesis of edema.

Mechanical obstruction. Venous obstruction was eliminated as a possible cause for the formation of edema by the finding of a pressure equivalent to 5.5 cm. of water in the left femoral vein. Lymphatic obstruction was excluded by the absence of a history or clinical evidence of an inflammatory lesion in the lower extremities; also, there was no evidence of lymphangiitis at any time.

"Sodium-Retaining" Edema

Hyperadrenocortical function (with increased secretion of salt-retaining steroids). The average daily urinary excretion of 17-ketosteroids was 30.5 mg., determined on a pooled, six-day collection; this was twice the normal output. In addition, as mentioned above, the daily urinary excretion of sodium appeared to be less than the dietary intake. Thus, the data suggested sodium-retention associated with increased adrenocortical function. Further evidence for increased adrenocortical function was provided by the persistent hypokalemia, which could not be corrected by the oral administration of potassium salts. Possible causes for the increased adrenocortical secretion of salt-retaining steroids included adrenocortical hyperplasia, which was reported on microscopical examination of post-mortem sections of the adrenal glands.

Renal disease. There was no evidence that renal insufficiency was the basis of the sodium retention in this patient. The concentrations of blood urea nitrogen and serum creatinine were normal on admission, and the endogenous creatinine chromogen clearance was 100 cc. per minute early in the hospital course, although it decreased later (probably as a result of dehydration). Microscopical examination of the urinary sediment revealed no gross abnormalities besides the presence of a few white blood cells.

Hepatic cirrhosis. The liver was hard and enlarged, but the only biochemical evidence of hepatic dysfunction was the bromsulfalein retention of 24 per cent; the determinations of serum bilirubin, globulin, alkaline phosphatase and cephalin flocculation were normal. Thus, intrinsic disease of the liver must be excluded as a cause for sodium retention.

Cardiac disease. What is the evidence for cardiac disease (such as congestive heart failure) as a contributing cause to sodium and water retention, with consequent formation of edema, in this patient? The electrocardiogram suggested arteriosclerotic heart disease (small Q and low T waves in Lead 1, small Q wave in Lead aVL and isoelectric T wave in Lead V_5. Although the venous pressure (in the arm) was equivalent to 4.5 cm. of water, the circulation time, measured with Decholin, was 18.5 seconds. Of additional interest is the development of pulmonary edema during the Hickey–Hare test despite the fact that the urinary flow exceeded the volume of fluid administered; this must be considered indicative of underlying cardiac disease, and possibly of (latent) congestive heart failure.

In summary the retention of water appears to have been secondary to that of sodium. The probable causes of this sodium retention are increased adrenocortical secretion (of "salt-retaining" steroids) and congestive heart failure.

Serum Electrolytes

The patient's persistent hypokalemia has been discussed, and ascribed to hyperadrenocortical function.

There was a large tumor nodule in the left frontal lobe of the cerebrum, raising the question of a possible relation of this lesion to the hypernatremia and hyperchloremia. Welt and his associates[7] have summarized

the literature on the relation of lesions of the central nervous system to hypertonicity of body fluids, and Engstrom and Liebman[8] have also discussed this subject. Available evidence is inadequate to establish that cerebral lesions can produce hypertonicity of the body fluids in patients who are not suffering from diabetes insipidus. It seems that such lesions may cause dehydration, with resulting hypertonicity of the body fluids, if they impair the thirst mechanism, producing insufficient ingestion of water. In the case reported above, there was no impairment of the thirst mechanism, and it therefore seems probable that the hypernatremia and hyperchloremia resulted from dehydration because of excessive urinary loss of water. Further support for this premise is provided by the fact that Pitressin therapy restored the serum concentrations of sodium and chloride to normal.

Hickey–Hare Test and Development of Pulmonary Edema

The patient presented signs and symptoms of pulmonary edema after receiving 429 cc. of 2.5 per cent sodium chloride at a rate of 16.5 cc. per minute for twenty-six minutes. During the same period the rate of urinary flow was 24.3 cc. per minute for fifteen minutes and 20.9 cc. per minute for eleven minutes; therefore, although the patient was in negative water balance during the saline infusion, there may have been a local (pulmonary) osmotic shift of fluid from the cellular to the extracellular and blood compartments. This possibility is supported by the fact that the serum concentrations at the time of discontinuance of the saline infusion were not higher than the control values when the hydration studies were begun.

A word of caution may be given at this point concerning use of the Hickey–Hare test,[5,6] involving the rapid, intravenous administration of hypertonic saline solution to older people who may be suffering from arteriosclerotic heart disease.

Terminal Phase

This period was characterized by irreversible shock, presumably brought on by extensive destruction of each adrenal medulla by metastatic tumor growth. Levophed was therapeutically effective only for a limited period, at the end of which the patient died.

Summary and Conclusions

A case of diabetes insipidus caused by metastatic neoplastic destruction of the posterior lobe of the pituitary gland, the original lesion being a bronchogenic carcinoma, is presented. In addition massive edema of the lower extremities developed on the probable basis of sodium retention, secondary to adrenocortical hyperfunction and congestive heart failure. Hypokalemia was an associated feature of the patient's course. The hypernatremia and hyperchloremia observed are believed to have resulted from dehydration, and were corrected by Pitressin therapy.

The physiologic significance of this case lies in the demonstration that water retention and edema formation may occur in the virtual absence of the neurohypophyseal antidiuretic hormone. Such a finding concerns the broader problem of the role of the antidiuretic hormone in the production of edema in hepatic and cardiac disease. It is concluded that the antidiuretic hormone may be a contributing but not a necessary factor in the retention of water with subsequent edema formation.

I am indebted to Drs. Martin Kurtz and Howard Moskowitz and Mr. George Rubin for their aid in the management and study of this patient.

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VULVAR FUSION IN INFANCY AND CHILDHOOD

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VULVAR fusion or agglutination of the labia minora is reasonably frequent[1,2] in infancy and childhood. This entity, of particular importance to the family physician and pediatrician, has been discussed chiefly in urologic journals[3] and has received scant attention over the past fifteen years in the general medical literature[4-6] of the United States.

Vulvar fusion goes unnoticed unless routine inspection of the genitalia is an integral part of the well-baby examination. Failure to recognize this condition, particularly in later childhood and adolescence, leads to erroneous diagnoses, often of disturbing psychologic import. On the other hand recognition in early infancy affords simple and complete correction.

Vulvar fusion, which has a varied nomenclature (atresia of the vulva, synechiae of the vulva, occlusion of the vaginal vestibule, acquired gynatresia and adherent labia minora), was originally described in 1936 by Nowlin and Adams[1] in their presentation of 8 cases. This report was followed by Campbell's[4] description of 9 cases. It is important to note that this author remarked that the physicians who originally saw the patients thought that they were dealing with hermaphrodites or pseudohermaphrodites. Excellent reviews on the subject have since been presented by Bowles and Childs[2] and Nowlin, Adams and Nalle.[3]

The etiology is controversial. Campbell[4] considers vulvar fusion to be of embryologic origin, but Bowles and Nowlin believe that it is brought about by the richness in cellularity of the labia minora and the close approximation of these structures in early infancy and childhood. This close approximation, particularly in the posterior portion and often associated with mild inflammation, could easily result in an agglutination of these structures without any marked signs of vulvitis.

DISCUSSION

The frequency of vulvar agglutination is variable. One group reports 110 cases in fourteen years,[3] whereas another[2] states that 20 children were treated for this condition within a year. It is my opinion that one sees 6 to 12 cases a year that require follow-up treatment.

There are usually no symptoms except in older children, who may have signs and symptoms of acute pyelocystitis. Diagnosis is made by routine physical examination of the genitalia. When the labia majora are separated the labia minora are seen to be sealed together by a thin, gossamer-like, semitransparent membrane, which bulges perceptibly during urination. Anteriorly, there is a small pin-point opening just below the clitoris through which the urine emerges.

The chief reason for this paper is to emphasize the fact that in the routine examination of all newborn female infants the genitalia should be included in the parts to be examined, and that in well-baby follow-up examination a quick and cursory glance at the genitalia should be a matter of course. Likewise, in the older child, up to and including age seven to nine years, the genitalia should be examined with the child lying with thighs widely separated to permit deliberate inspection of the vulva.[2] A recommended procedure in preadolescent and adolescent children is the examination of the vulvar structures in the knee-chest position as an essential part of the examination of the anorectal region.

Prophylactic treatment is simple. Parents of very young infants are instructed in the use of a bland or analgesic ointment to keep the labia minora separated. If the membrane, in the older child, is thin this type of treatment is sufficient. However, if the membrane is thickened or adherent it is strongly recommended that light anesthesia be administered so that the agglutinated membranes may be separated without undue psychologic trauma.

It is reasonable to speculate that this condition, in most cases "takes care of itself." On the other hand a laissez-faire attitude or the reluctance of a physician to examine the genitalia of female infants and young children occasionally permits a situation to develop that could have been handled easily by the simple prophylaxis of a routine examination.

CASE REPORTS

It is not the purpose of this paper to list the number of cases of this condition seen in a general pediatric practice but rather to present clinical examples of it as it concerns the infant and the young girl and her parents.

CASE 1. M.G., a 6-week-old girl, was examined routinely and inspection of the labia minora disclosed a thin, gossamer-like membrane covering the posterior aspect of the labia. The parent was informed of the nature of the membrane and given instructions for its treatment. The infant, after her bath, was to be placed in a "frog's legs" position. The mother, upon separating the labia with the thumb and index finger of the left hand, pressed down with her right hand, using cotton-tipped toothpicks covered with an analgesic or simple ointment such as petrolatum, with gentle and sustained pressure on the base of this membrane. Daily treatment was advised for the 1st week. Thereafter, at intervals of 2 or 3 days there was a gradual decrease in frequency of treatment so that at 3 months of age the membrane had disappeared and treatment was stopped.

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CASE 2. B.C., a 2-month-old infant, had a more tenacious membrane than that described in Case 1. This membrane occluded the vaginal vault and extended upward to just below the urethral opening. She was examined by the family obstetrician and a pediatrician who believed the membrane would take care of itself in later life and did nothing about it. At 2 years of age, because of painful urination and persistence of and further thickening of this membrane, the patient was examined by a urologist, who thought she might have a genital aberration. He therefore suggested that a colleague of his, expert in deviations of sexual anatomy, be consulted. Disturbed by such advice the parents had the patient examined by another pediatrician, who recognized the condition and separated the labia without any anesthesia, using blunt dissection. He advised follow-up treatment with sitz baths and an analgesic ointment to the raw surfaces. The infant had a marked reaction to this handling, and for 1 week later she refused to urinate unless she was placed in a warm bath. At the age of 4½ years she was still fearful of any examination or bathing of her vulvar region. There was an occasional redness of the labia that required simple treatment, but there had been no further agglutination.

CASE 3. C.E., a 4-year-old girl, was examined because of enuresis. She had a slightly thickened vulvar membrane extending up to the level of the urethral opening. There were no presenting genitourinary symptoms aside from the enuresis. There was evidence of tensional difficulties. Urine specimens were normal on examination.

It was suggested, in view of the experience in Case 2, that the patient be hospitalized for treatment. The mother was quite upset by this recommendation and wanted other medical opinion.* The child, in turn, saw a urologist, who believed he was dealing with a pseudohermaphrodite and refused to handle the case, and a gynecologist, who also was quite sure she had an anatomic deviation. The mother was then persuaded by her family physician to follow my advice. The patient was admitted to a hospital, where, under nitrous oxide anesthesia and simple blunt dissection, the labia were separated readily. Inspection of the genitalia at time of operation revealed a normal vaginal vault and introitus. There has been no recurrence to date. Enuresis has persisted.

*The mother had had a similar condition, of which she was unaware, that persisted through adolescence. At the time of a premarital examination she was advised not to marry because this "abnormality" precluded sexual intercourse. Fortunately, she was examined by another physician, who treated her successfully. She had given birth to 3 normal children.

CASE 4. P.F., a 4½-year-old girl, was referred for examination because of dysuria, urgency, lassitude and a rise in temperature to 102.6° F. Examination of the external genitalia revealed an inflamed urethral orifice associated with an adherent cul-de-sac vulvar membrane. Simple sitz baths and antibiotics corrected the cystitis. Once, during a strenuous effort to re-examine the vulvar area, the membrane separated spontaneously. After the acute illness the parent was instructed to apply an analgesic ointment. There has been no recurrence in the past 2 years. Urine samples have been examined at 6-month intervals, and all specimens have been normal.

CONCLUSIONS

Vulvar fusion, or agglutination of the labia minora, is reasonably frequent in infancy and childhood. This entity, which is of minor import in infancy, is disturbingly significant in childhood and adolescence. The routine examination of the vulvar structures in the general examination of the newborn female infant and a continuance of this procedure in later infancy and childhood is recommended.

10 Main Street

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KING EDWARD'S HOSPITAL FUND FOR LONDON

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LONDON, ENGLAND

IT was 1897, and London, like all Her Majesty's dominions, was preparing to celebrate the Diamond Jubilee of the accession to the throne of Queen Victoria. On January 21, under the chairmanship of the Prince of Wales (later King Edward VII), a meeting was held at Marlborough House to decide whether the creation of a central hospital fund for London was a suitable method of commemorating the historic occasion. Among the twenty-two distinguished leaders of London life who attended the meeting were Sir Joseph Lister (later Lord Lister), as president of the Royal Society, Dr. Samuel Wilks, as president of the Royal College of Physicians of London, and Sir William MacCormac, as president of the Royal College of Surgeons of England. The royal chairman informed the meeting that his mother warmly approved of the suggestion, and after a full discussion of the project, it was unanimously decided to create such a fund in commemoration of the Diamond Jubilee. All those present were constituted a general committee. When this committee met again a fortnight later, "The Prince of Wales's Hospital Fund for London to Commemorate the Sixtieth Year of the Queen's Reign" was formally inaugurated (Fig. 1).

*Editor, *The Practitioner*.

THE EARLY DAYS

Thus was constituted an organization that during the subsequent sixty years has played a role of ever-increasing importance in the development of the hos-

pital services, not only of the metropolis but also of the entire country. Its history mirrors in striking detail the transformation that the hospitals of the country have undergone in the period intervening between the reigns of Queen Victoria and her great-great-granddaughter, Queen Elizabeth II.

On February 5, 1897, all the London morning and evening newspapers (Fig. 2) published a letter from

FIGURE 1. *The Jubilee Hospital Stamp, Specially Issued as Part of the Inaugural Appeal for the Prince of Wales's Fund. The plates from which the stamps were printed were ceremoniously destroyed at the Bank of England on July 9, 1897, in the presence of the Duke and Duchess of York (later King George V and Queen Mary). The sale of these stamps realized £34,776.*

the Prince of Wales, appealing for contributions to the Fund. In his letter he pointed out that the audited accounts for 1895 of 122 metropolitan hospitals and convalescent homes showed a deficiency of £70,000 in the ordinary receipts as compared with the ordinary expenditure, and that less than one in a hundred of the population of London were contributors to the funds of these hospitals. "Our attention will be concentrated upon an endeavour to secure from £100,000 to £150,000 in annual subscriptions from those who have not regularly contributed." In view of what has transpired since those halcyon days it is of interest to note what His Royal Highness had to say about the voluntary system:

> Public opinion has shown itself upon more than one occasion, and I think wisely, in favour of the maintenance of the voluntary system for support of our hospitals. . . It is obvious, however, that if these institutions are to be saved from State or parochial aid, their financial condition must be secured.

By the end of the year the Fund had received a total of £227,562. Before consideration of the policy followed in the distribution of the income of the Fund, the history of the Fund during the next few years should be summarized. On the death of Queen Victoria in January, 1901, King Edward VII was succeeded by his son, later King George V, as president. The accession of the new King was made the occasion for a special appeal for the Fund, and this brought in the sum of £123,829. In January, 1902, the name of the Fund was changed to the King Edward's Hospital Fund for London, by which it has ever since been known. In 1907 Parliament passed an act of incorporation for the Fund. One of the clauses in this act lays down that every president shall be a son, brother or grandson of the Sovereign, provided he is, in the opinion of the Lord Chancellor, the Prime Minister and the Governor of the Bank of England, duly qualified to fill the office. The appointment is made by the Sovereign and held during the Sovereign's pleasure. The subsequent presidents have been the Prince of Wales (later the Duke of Windsor), the Duke of York (later King George VI), the Duke of Kent, and the Duke of Gloucester, the President today, who was appointed to the office in 1942 on the death of his brother, the Duke of Kent.

Development of the Fund

From its inception, King Edward VII was insistent that the Fund should build up a large capital reserve and distribute to the hospitals only the income de-

FIGURE 2. *The Cartoon that Appeared in the* Daily Graphic *on February 9, 1897, as Part of the Publicity Campaign Announcing the Launching of the Inaugural Appeal for the Prince of Wales's Hospital Fund for London.*

rived from this capital. It is clear that in the early days of the Fund there was a not unnatural tendency to contest this injunction, but the fundamental soundness of the royal President's advice was always appreciated, and the subsequent history of the Fund has amply justified the policy. At the present day

the capital reserves are practically £7,000,000, which, in 1952, brought in an income of just over £340,000. This capital has come largely from munificent legacies, supplemented by periodic special appeals. Among the larger sums that the Fund has received throughout its history are £1,315,000 from Lord Mountstephen, £526,000 from Mr. Samuel Lewis, £483,000 from Sir Thomas Sutherland, £420,000 from Mr. Claude Watney, £390,000 from Sir Julius Wernher, and £100,000 from Mr. Andrew Carnegie. As the amount distributed annually has increased from £22,050 (in addition to a special Jubilee donation of £35,000) in the first year to the present total of over £300,000, so has the area covered by the Fund been gradually extended. In the early days of the Fund its distribution was restricted to the 97 hospitals and convalescent homes within a 7-mile-radius of Charing Cross. It now covers the whole of the Metropolitan Police Area, with its 168 hospitals.

Scope of the Fund

The purpose of the Fund, according to the Act of Incorporation, is "for the support, benefit or extension of the hospitals of London." Although the Fund, throughout the years, has taken full advantage of the scope allowed to it under these wide terms, it has never stressed the letter of the law at the expense of the spirit. As in his interpretation of its financial policy, its first President had very clear ideas of what the Fund should, and should not, do. These can best be illustrated by two quotations from addresses that he made to the Grand Council in 1897 and 1898:

> It will never do for us to give money right and left to hospitals which are in need. It will be necessary for us to investigate the state in which these hospitals are, to find out those which are in most pressing need of assistance, and also to form some opinion as to the state of efficiency in which they at present exist and how the management is carried on. . . . Unfortunately, as you must be well aware, in many cases wings and wards are now built when the hospitals can only hope that future charity, by means of dinners and bazaars, may give them the assistance necessary to defray expenses; and if they do not receive as much money as they hope from these bazaars and dinners they are ultimately obliged to close the very wards which they recently opened. It is this extravagance in the maintenance of hospitals which this Fund should endeavour to discourage.

To ensure that these aims should be attained and maintained, "visitors" were appointed by the Fund to visit the London hospitals and report on their organization and need for support. These "visits," by degrees, developed into one of the most important factors in the gradual improvement in the organization, accountancy and efficiency of the London hospitals. The "visitors" consisted of one medical man, one layman and, later, an official of the Fund. Although somewhat "suspect" in the early days, they carried out their work with such tact and care that it was not long before they were welcomed by the hospitals for the advice and information that they could provide, not only on the efficient maintenance of the hospital but also on its possible developments. Only a few of the reforms introduced as a result of their activities can be mentioned here.

The amalgamation of hospitals to attain increased efficiency has always been one of the aims of the Fund, and as early as 1903 it was able to bring about the amalgamation of the National and Royal Orthopaedic hospitals under the title of the Royal National Orthopaedic Hospital, which was joined three years later by the City Orthopaedic Hospital. Improved hospital accountancy was another of the Fund's early aims, and in 1906 it issued a "Revised Uniform System of Hospital Accounts," the adoption of which was made a condition of any future grant from the Fund. A policy of particularly large immediate grants for specified purposes has been followed for many years. One of the first of these was a grant of £10,000 to Guy's Hospital, in 1907, to facilitate the building of a badly needed outpatient department. In the same year the Fund instituted an inquiry into ways and means of helping hospitals to improve their protection against fire, and the Fund's "Suggestions for Protection against Fire," revised at frequent intervals, has remained the standard work on the subject for the London hospitals. In 1914 an inquiry was instituted into the possibility of providing a pension scheme for nurses and hospital officers. World War I delayed action in the matter, but in 1928 the "Federated Superannuation Scheme for Nurses and Hospital Officers (Contributory)" was inaugurated. The scheme covered not only London but the whole country, and provided for all salaried staff, administrative, financial, clerical and dispensing, all female nurses and student nurses after their first year of training. As a token of its practical interest in the scheme, the Fund made a special grant of 25 per cent of the initial cost to hospitals up to a maximum of £20,000 annually for seven years.

Finally, brief reference should be made to the Fund's contribution to the development of radiotherapy in this country. In 1928 it undertook the responsibility for improving the deficient radium supplies of the London hospitals. Largely owing to the generosity of Sir Otto Beit, it had provided 4 gm. by the end of the year. During the following years this amount has been more than quadrupled. That this interest is being maintained is shown by the fact that toward the end of 1953 it was announced that the Fund had made a contribution to the cost of the 15,000,000-volt linear accelerator that is being installed at St. Bartholomew's Hospital — "the most powerful machine for x-ray therapy at the present time."

The Fund Today

The annual report of the Fund for 1952 shows that the expenditure in this year was £413,760. This in-

cluded £100,000 for homes for the aged sick, £140,000 for hospitals, £30,000 for convalescent homes not attached to hospitals, £21,000 for the division of hospital facilities, £22,000 for the division of nursing, £23,000 for the hospital catering and diet committee, £24,000 for the hospital staff administrative-staff college, £2,500 for bursaries for almoners and £6,500 for the emergency bed service. The sum allotted to hospitals and institutions outside the National Health Service was £43,000.

Perhaps the most significant developments in the activities of the Fund are the three staff colleges and the school of hospital catering that it now runs. The division of nursing includes a staff college for ward sisters that 89 ward sisters and staff nurses attended last year. This has now been supplemented by the opening of a staff college for matrons and prospective matrons. Both these colleges are residential, and the aim is to broaden the outlook of senior nursing staffs by allowing them to meet their contemporaries from other hospitals and to visit other hospitals. For the matrons, "much of the time will be devoted to practical experience in industry as well as within the hospital world, studying the tasks, aims and methods of men and women carrying administrative responsibilities and the reactions of the staff to those methods."

The hospital administrative staff college, which is also residential, was opened in 1951. Its major activities consist of two types: a one-month refresher course for hospital-group secretaries, and similar courses for hospital secretaries. So far, over 200 hospital officers have participated in these courses. The other is a two-year training course, the first of which was begun in March, 1952, attended by seven men already employed in hospital service.

The school of hospital catering, situated in St. Pancras Hospital, was established in 1951. It runs refresher courses for catering officers, kitchen superintendents, head chefs and cooks, and 139 students passed through the school in 1952. An innovation in 1952 was the introduction of a year's course for prospective catering officers. Eight bursaries, valued between £400 and £500, were offered, and the eight recipients will spend part of their time at the school and part at selected hospitals in the London area. Associated with the school is a hospital catering advisory service, which is being used to an increasing extent by the London hospitals for advice on their catering problems.

Emergency Bed Service

In 1937 the Fund inaugurated a scheme that has proved a boon to the general practitioners of London. This is called the Emergency Bed Service and consists of a central office that is staffed throughout the twenty-four hours. If a practitioner has an emergency case that he wishes to be admitted to a hospital, he need no longer spend a frantic hour (or hours) telephoning a series of hospitals until he finds one that will take his patient. All he need do is telephone the Service, giving the relevant details of his case, and the Service then makes the necessary arrangements for the patient to be admitted to a hospital as near as possible to his home (Fig. 3). This it does by maintaining an up-to-date list, revised daily, of all the vacant beds in the London hospitals.

By PHILIP EMBEY. F.R.C.S., M.R.C.O.G.,
How the Emergency Bed Service works
The doctor wants a hospital bed urgently for Mrs. Brown. He phones the Emergency Bed Service.
The watch-keeper notes down that this is a case of pneumonia in an old lady.
All nearby hospitals are tried until a bed is found at the Cricklewood Hospital.
The hospital is now ready to receive Mrs. Brown. The ambulance is seen there.
Thirty-five minutes after the first telephone call Mrs. Brown is in hospital.

FIGURE 3. *Drawings Showing the Working of the Emergency Bed Service (Reproduced from the* Family Doctor *for January, 1954, with the Permission of the Publishers).*

The Service proved to be so popular with general practitioners that in January, 1951, 7064 applications were received for help. Since only 65.5 per cent of these patients could be admitted to hospitals a "warning system" was introduced: when the ratio of admissions to applications, calculated on the moving weekly totals, falls below 85 per cent, a "white" warning is sent to the appropriate hospital authorities. This in effect means that the Service is hard pressed and may be in serious difficulty in the next day or two. If the admissions fall below 80 per cent, a "yellow" warning is issued, and if below 75 per cent a "red" warning. These mean that the situation is serious, and that for 1 patient in 4 or 5 no bed can be found. On receipt of these warnings the hospitals take prearranged action to provide more accommodation for emergency admissions. This warning system received its first major trial during the London smog of December,

1952, when on one day alone, December 9, applications were received for 492 admissions. The system worked without a hitch, and has obviously come to stay as a permanent feature of the London hospital service. During the five winter months of 1952-53, 33,786 applications were received, or approximately 225 every day.

The Future

When the history of the King's Fund comes to be written, as written it must be, it will constitute an outstanding memorial to the achievements of the London hospitals during the last fifty years of their existence as voluntary institutions. In the attainment of these contributions to the health and welfare of the citizens of the metropolis, the King's Fund has played a decisive part. The glory of the voluntary system is that co-operation does not mean loss of individuality, and in achieving co-operation without loss of personality the Fund has performed a role for which Londoners can never be grateful enough.

The introduction of the National Health Service, however, has raised new problems, and, courageously as the Fund has faced them, there are some who question whether the vast sums now at its disposal are being expended in accordance with the aims and wishes of the founders of the Fund. What, ask these friendly critics, is the function of a fund such as this in a state medical service? Is it to subsidize services that the State should provide, or is it to provide ancillary services for those who wish to maintain the voluntary spirit in these days of nationalization? This is not the place to attempt to answer these questions, but it is pertinent to point out that during 1953 the Fund allotted more than twice as much to National Health Service hospitals as to voluntary hospitals outside the Service: £73,000 as opposed to £35,000. In a country with a national health service, is it necessary, the critics ask, for a fund such as the King's Fund to present £1,290 to the National Health Service to meet the cost of a new diet kitchen in one hospital, £2,000 for the provision of refrigerators and lockers in another, and £2,400 for the cost of electrically heated trolleys in yet another?

As the "old order changeth, yielding place to new," there is bound to be an awkward transition period. The adjustment is no more difficult for the King's Fund than for the medical profession itself. Considerable imagination and initiative have been shown in its plans to support homes for the aged, convalescent homes and the efforts of the Royal College of Nursing to maintain the standards of nursing. It is along lines such as these, which do not fall strictly within the scope of the National Health Service, that it can most usefully continue to maintain the spirit of voluntary service and enterprise in a world of increasing uniformity.

MEDICAL PROGRESS

ESOPHAGEAL STENOSIS CAUSED BY PEPTIC ESOPHAGITIS OR ULCERATION*

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SINCE operations on the esophagus are now commonplace and since peptic stenosis of the esophagus is of great current interest to the internist, radiologist, endoscopist and thoracic surgeon, it seems appropriate to review this controversial subject and bring it up to date.

Etiology

Incidence

Vinson[1] found 40 cases of unknown origin among 243 patients with benign stenosis of the esophagus. Benedict and Sweet[2] reported 60 cases of what is now termed peptic stenosis among 1000 patients undergoing esophagoscopy. Of 1340 patients examined in this clinic, 119 (8.7 per cent) had peptic stenosis (100 of these being the basis of a recent report by Benedict and Gillespie[3]).

Sex and age. Of Vinson's[1] 40 patients with benign stricture of unknown origin, 17 were male and 23 female with ages ranging from six to seventy-five years. Benedict and Gillespie,[3] however, found a sex distribution of 60 males and 40 females. Allison[4] recorded 32 males and 27 females, in whom chronic ulcer and esophageal stenosis associated with hiatus hernia developed. Wilson,[5] in a report on stenosing peptic esophagitis, listed 18 males and 4 females, with ages from thirty-six to eighty-one years, 82 per cent being over fifty years.

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In 78 per cent of the 100 cases in the series of Benedict and Gillespie[3] the age at onset was between forty and seventy years — that is, at a later time than symptoms of peptic ulcer of the stomach and duodenum arise. The reason for this is believed to be that most patients with the ulcer diathesis do not generally have sufficient esophageal reflux to cause peptic stenosis until a hiatus hernia develops. The sex incidence shows a higher ratio of females to males than is usual in cases of peptic ulcer of the stomach and duodenum.

Significance of Gastric Juice

Clinical evidence.§ Tileston,[6] in a valuable article on peptic ulcer of the esophagus published in 1906, held that insufficiency of the cardia, allowing regurgitation of gastric juice, was essential for the development of the ulcer and hence that vomiting — as in peritonitis, ulcer of the stomach and duodenum and pyloric stenosis — was of importance. He reported 3 new cases of peptic ulcer and stated that the scarring of large esophageal ulcers resulted in esophageal stenosis.

Friedenwald, Feldman and Zinn,[7] in 1929, stated that, although patency of the cardia was essential for the development of peptic ulcer of the esophagus, which was sometimes followed by stricture, regurgitation of acid gastric juice alone was not sufficient but that some unknown factor was also necessary.

Lindau and Wulff,[8] in their classic article on the peptic genesis of gastric and duodenal ulcers published in 1931, considered that the central point of Buechner's theory was that the portion of the stomach producing gastric juice normally possessed a high resistance to its action whereas other parts had a relatively low resistance. Thus, there are more ulcers in the pyloric region than in the fundus, and ulcers can occur in the esophagus, the jejunum after gastroenterostomy and in a Meckel diverticulum when there is ectopic gastric mucosa. The authors demonstrated the great importance of gastric juice so far as it could cause ulceration in a Meckel diverticulum and that, by implication, abnormal gastric reflux into the esophagus or abnormal production by ectopic mucosa could result in ulceration.

In 1935 Winkelstein[9] described 5 cases of a new clinical entity called "peptic esophagitis" and held that the course of the disease, the location of the ulcers, the association with peptic ulcers, the hyperchlorhydria and the relief by ulcer treatment suggested the peptic origin of the esophagitis but that the mechanism was not entirely clear although it might be due to gastric juice retained in the lower esophagus by spasm of that organ. He thought that a nervous reaction might be responsible without peptic juice as a factor. In the discussion that followed this paper, Chevalier Jackson agreed that the cause of this type of esophagitis was also the cause of gastric ulcers but questioned whether gastric juice was the primary or the perpetuating factor.

Bartels[10] described the pathological and clinical findings in 82 cases of "acute ulcerative esophagitis" seen at autopsy and said that it was imperative to accept gastric juice as being contributory to the lesions since gastric juice was found in the lower esophagus in all cases; he pointed out the great importance of vomiting and even of nausea without vomiting but with relaxation of the cardia. Vinson and Butt[11] found esophagitis in 7 per cent of 3032 autopsies and emphasized the influence of vomiting and trauma from the use of stomach tubes.

Benedict and Daland,[12] in discussing a case of benign stenosis of the esophagus complicating duodenal ulcer, suggested vomiting and regurgitation of acid secretion as a possible cause of the esophagitis. Allison, Johnstone and Royce,[13] who presented 10 cases of peptic ulcer of the esophagus, all with cicatricial stenosis, considered acid gastric juice the most important factor although chronic infection also had to be considered. Bockus[14] included regurgitation of acid gastric juice among the theories of genesis of peptic ulcer of the esophagus and said that constitutional factors causing duodenal ulceration might be significant. Allison,[15] in a valuable paper on 74 cases of peptic ulcer of the esophagus, considered a hiatus defect, allowing regurgitation of acid gastric juice, the essential factor but believed that gastric juice would enter the lower esophagus from the use of a Souttar tube for malignant obstruction, the union of stomach and esophagus after excision of the cardia, paralysis or lack of tone of muscles in debilitated or dying persons and ectopic gastric mucosa. Olsen and Harrington,[16] in a report of 220 cases of esophageal hiatus hernias of the short-esophagus type, said that shortening occurred as the result of peptic ulceration of the esophagus from excessive or prolonged vomiting or incompetence of this physiologic sphincter. Olsen[17] regarded reflux of gastric juice as the most common cause of esophagitis and stressed the influence of vomiting and incompetence of the cardia from such conditions as hiatus hernia. Benedict and Sweet,[2] reporting 60 cases of benign stricture of the esophagus, held that regurgitation of acid gastric secretion was probably an important cause of esophagitis and benign stenosis. Barrett[18] considered reflux esophagitis to be common and capable of giving rise to ulceration of the esophagus and stricture formation. Wilson[5] described 22 cases with reflux of acid gastric juice as the probable cause. Friedberg and Clayton,[19] in a report of 6 cases, observed that all the patients had the peptic-ulcer diathesis and that esophagitis could occur from reflux of acid gastric juice.

Many other reports supporting the thesis of the harmful effects of gastric juice on the lower esophagus have been reviewed, but enough have been cited to give some idea of the volume of clinical opinion. But not every case with regurgitation manifests an eso-

§Articles are considered in chronologic order.

phageal lesion; for example, Allison[4] mentions a patient who had a sliding hiatus hernia with regurgitation for over fifty years but no esophagitis.

In the series of Benedict and Gillespie[3] there had been vomiting, often of marked degree, in 29 cases before dysphagia began, the causes being peptic ulcer of the duodenum or stomach in 5, pyloric stenosis in 5, unknown in 5, postoperative complication in 3 and pregnancy in 1.

In addition vomiting or regurgitation probably occurred in 6 alcoholic patients and in 1 patient who was comatose and severely ill with jaundice and myocardial infarction in another hospital; 14 patients had had gall-bladder disease and, although vomiting was not severe in any of these, it may have occurred at times. We believe that the presence of acid gastric juice in the esophagus is an essential feature for the development of this type of stenosis. The circumstances that allowed gastric juice to remain for an abnormal time in the esophagus in the other cases are considered below.

Experimental evidence. In 1938 Selye[20] described the production of what he called hemorrhagic esophagitis by pyloric ligation in rats, indicating that the presence of gastric juice for an abnormal time in a normal esophagus would produce inflammation. He considered that the occurrence of esophagitis in debilitated human patients was more probably due to regurgitation of peptic juice rather than to weakening of the resistance of the esophagus.

Ferguson et al.,[21] in experiments on various types of animals, found that acid gastric juice in contact with the esophagus for an abnormal time, whether from vomiting or regurgitation or by direct application, had a "devastating effect" whereas hydrochloric acid in similar concentration to that in gastric juice had little influence by itself. When bile or pancreatic juice was added to the gastric fluid, the injurious action was considerably reduced. The authors observed that living and dead tissue responded in much the same way and so concluded that the blood circulation of this part was not involved. They believed that these experiments "favour the idea that nonspecific esophagitis is due primarily to the action of acid-peptic juice." Arroyave, Clatworthy and Wangensteen[22] produced inflammation and ulceration experimentally by means of gastric transplants in the esophagus (in some cases, histamine had to be given as well). They believed that heterotopic gastric mucosa in the human being could produce significant amounts of gastric juice that would act on the esophageal mucosa while the cardia was closed. Ripley and his associates,[23] in experiments on 4 dogs with a Heidenhain pouch and 5 with an esophagogastrostomy, caused ulceration and stricture formation.

The conclusions from these experiments, which obviously cannot be applied wholesale to man, are in agreement with the thesis that acid gastric juice is harmful to the lower esophagus in human patients.

Significance of Ectopic Gastric Mucosa in the Esophagus

This is a more controversial and less well documented subject than the question of the harmful effects of gastric juice. Although isolated islets of gastric mucosa surrounded by esophageal tissue are undoubtedly ectopic, it appears that the line of junction between the esophageal and the gastric is often irregular so that tongues of gastric mucosa may project upward and tongues of esophageal mucosa may project downward. An associated difficulty is that the cardia is a somewhat ephemeral concept better recognized physiologically than anatomically.

Schridde,[24] in 1906 (cited by Lerche[25]), found acid maceration of the upper cardiac glands in the esophagus identical with the condition frequently observed post mortem in the stomach from acid action. Lindau and Wulff[8] reported 2 cases of peptic ulcer in a Meckel diverticulum arising from ectopic gastric mucosa and collected 35 cases from the literature; although conditions are not strictly comparable, this suggests that ulcers could arise in a similar manner in the esophagus. The experimental results with gastric transplants referred to above also suggest the possible importance of ectopic mucosa although it is questionable if similar amounts of gastric juice are secreted in the human esophagus. Barrett[18] says that the islets are generally very small and very high and that he does not believe that "the tiny volume of acid, diluted by pints of saliva would be likely to harm the lower reaches of the gullet."

Allison, Johnstone and Royce[13] discussed the question of regurgitation of gastric juice as opposed to its production by ectopic mucosa, advising caution in ascribing importance to heterotopia since scarring may draw up gastric mucosa and, after dilatation of the cardia, the gastric mucosa may protrude into the esophagus and be included in a biopsy. The same authors state that Schridde[26] on routine histologic examination of all bodies found 70 per cent to have gastric glands in the esophagus. In a later article Allison[15] considered that certain cases of peptic ulcer of the stomach associated with a long stenosis were probably caused by heterotopic mucosa and again that an extreme degree of gastric heterotopia might occur so that the lower esophagus would be lined with gastric mucosa but that, although suspected in some of his cases, this had never been satisfactorily proved. Since then Allison[27] has observed clear evidence of a gastric lining in some cases of peptic stenosis of the esophagus with gastric ulcers in that area and some with esophageal ulcers above. Bosher and Taylor[28] reported an interesting case that appears similar to those referred to by Allison. In this patient the lower half of the esophagus was lined with gastric mucosa. A resection and esophagogastric anastomosis were done. The authors state that it was not a thoracic stomach and short esophagus since there was a small, easily reducible hernia and "at operation the entire

stomach lay below the diaphragm." Redish and Kertzner[29] described 6 cases of peptic ulcer of the esophagus, in all of which ectopic gastric mucosa was noted in one or more biopsy specimens. Forty-nine of the 80 patients in the series of Benedict and Gillespie[3] who had a biopsy taken showed gastric mucosa in one or more specimens. Certainly, in some of these cases and probably in all (as discussed below) the biopsy was taken from near the cardia. The invariable inflammation and the anatomic deformity mean that estimation of the exact site of the biopsy in relation to the cardia is sometimes difficult. However, in most cases of specimens resected at operation it was noticeable that there was no inflammation of the adjacent gastric mucosa, and none showed ectopic gastric mucosa of any significant extent in the lower esophagus.

Site of Stenosis in Relation to the Cardia

This is a point of great importance, for, if gastric juice is the main factor, the lesion is likely to occur just above the cardia. If all or probably all lesions occurring in this region and their peptic genesis are not accepted some other theory will have to be advanced for this particular location. It may be suggested that the area is more vulnerable to trauma from ingested food because of the anatomic arrangement and the delay in the passage of the bolus.

Vinson,[1] reporting 40 cases of stenosis, said that the lesion was in the upper third in 9 (8 to 25 cm. from incisor teeth), in the middle third in 10 (28 to 33 cm. from the incisor teeth) and in the lower third in 21 (35 cm. from incisor teeth to cardia). These were all clinical estimations, and the site of the cardia was not stated. Kelly[30] observed that in 2 cases of constriction associated with congenital shortening of the esophagus the junction of esophagus and cardia was close to the lower end of the stricture. Clerf and Manges[31] found the narrowing to be at the esophagogastric junction in 14 cases described under the heading of "congenitally short esophagus." Allison[32] reported that in 74 cases of peptic ulcer of the esophagus, the lesion was always immediately above the gastric pouch. Wilson[8] described the narrowing as just proximal to the esophagogastric junction on clinical examination in 22 patients. Many other authors have implied that the lesion was just above the cardia, but it is obviously essential to determine the region affected as accurately as possible.

Radiologic examination, which generally shows the relation, can sometimes be misleading. In 1930 Kelly[30] pointed out that in children with so-called congenital esophageal constriction the structure below the lesion was stomach and not esophagus. Allison[15] demonstrated the difficulty, at times, of determining if dilatation below a lesion was esophagus or hiatus hernia; he applied clips to the esophagogastric junction and then took x-ray films to show the exact relation. At esophagoscopy the relation may be obvious, but in some cases it may not be clear, especially if the stenosis cannot be dilated to allow the passage of the esophagoscope.

Significance of Acquired Esophageal Hiatus Hernia

In 1946 Benedict[33] reported that, of 44 patients with benign stenosis of the esophagus, 7 had hiatus hernia, and later Benedict and Sweet[2] found that of 60 patients with benign stenosis 34 had a hiatus hernia (some of these cases are included in the series of Benedict and Gillespie[3]).

The incidence of esophageal obstruction in known cases of hiatus hernia has been noted by several authors. Thus, Olsen and Harrington[16] discovered that of 220 patients with a "short esophagus" type of hiatus hernia, 154 had actual obstruction as shown by esophagoscopy or the passage of a bougie. (These 220 patients represented 10 per cent of those with hiatus hernia of all types). Clerf and Manges[31] stated that of 110 patients with esophageal hiatus hernia, stenosis was present in 18 as shown by esophagoscopy. Allison[4] reported that 63 of 176 patients with sliding hernia had stenosis.

Allison has been responsible for showing the great importance of hiatus hernia in the production of peptic ulcer of the esophagus and subsequent stenosis. He proposed this theory in 1946,[32] and added that 37 cases of proved peptic ulcer of the esophagus associated with diaphragmatic and gastroesophageal insufficiency had been seen. He outlined the course of the disease as follows:

> Regurgitation of gastric juice → inflammation of esophagus → ulceration → fibrosis → stricture formation.

In 1948 Allison[15] pointed out that the so-called "short esophagus" is usually an acquired condition resulting from an esophageal hiatus hernia that, by allowing regurgitation, eventually results in contraction of the esophagus in a circumferential and lengthwise direction.

The incidence of hiatus hernias as found on radiologic examination is, of course, high; the anomaly occurred in 8.9 per cent of 3448 patients examined by Brick[34] for digestive symptoms and in 3.5 per cent of 1500 patients observed by Turner.[35] Root and Pritchett[36] recorded an incidence of 1.37 per cent in all patients examined. The older the group of patients, the higher the proportion with hernias, but one must take several facts into consideration to assess the significance of the finding. The first point is the type of hernia. The paraesophageal ones do not allow regurgitation unless the cardia is also involved. A small, sliding esophageal hernia may be present only when there is increased abdominal pressure, and so the amount of reflux may be insignificant. Even with a permanent esophageal hernia, the physiologic sphincter at the cardia may be sufficient without diaphragmatic help to prevent serious regurgitation into the esophagus.

Congenital short esophagus with partial thoracic stomach—that is, not a true hernia but failure of the stomach to leave the thorax and consequent deficiency of the diaphragm—has often been diagnosed in the past but very much less frequently at present. Olsen and Harrington[16] considered that it formed 4 per cent of their series of 220 cases of short esophagus, and Allison[15] found 7 cases among 74 cases of peptic ulcer of the esophagus. In the series of Benedict and Gillespie[3] there were 3 cases that were probably of congenital origin. This disability, like acquired hernias, allows reflux of gastric juice, but dysphagia develops at a much earlier age.

According to Thomsen[37] the coexistence of peptic ulcer of the esophagus with short esophagus was first described by Haroen and Gerlings.[38] A few years later Briggs, Dick and Hurst[39] reported 8 certain and 5 probable cases of peptic ulcer of the esophagus with short esophagus and held that esophageal ulcer was always associated with a "hernia" due to a congenitally short esophagus.

What had previously been diagnosed as "congenital" short esophagus has been shown to be an acquired condition in a large proportion of cases. Briefly, a survey of the articles by Johnstone,[40] Allison, Johnstone and Royce,[13] Olsen and Harrington,[16] Allison[15] and Smithers[41] demonstrates that they believe that lengthwise contraction of the esophagus follows irritation of the esophageal mucosa by gastric reflux. Thus, by the time the patient seeks advice, he normally has an acquired short esophagus. The objection may be raised that the hiatus hernia is secondary to the contraction of the esophagus diseased from some cause but not necessarily from gastric reflux. It is certainly true that some patients are seen with esophageal stenosis and a long or even redundant esophagus (1 case in the series of Benedict and Gillespie[3]), and it is known that many patients have had hiatus hernias for years before stenosis develops but adequate figures to settle this point are lacking. However, we believe that the available data suggest that stenosis generally follows rather than precedes the development of a hiatus hernia.

Question of Reflux Shortening of the Esophagus

Gilbert, Dey and Rall,[42] discussing recurrent hiatus hernia, considered Bergmann's[43] hypothesis of vagal stimulation by lesions in the upper abdominal viscera a reasonable explanation and found that 27 of these patients had a possible source of stimulation, such as cholelithiasis, duodenal ulcer and esophageal diverticula. In another paper Dey and his associates[44] described the experimental production of hiatus hernia by electric stimulation of the vagus nerve (as had been done by Kukluck according to Bergmann) or by manual stimulation of the upper abdomen. Robins and Jankelson,[45] in 1926, found gastrointestinal lesions in most cases of "cardioesophageal relaxation" (103 patients were included, of whom 26 had gall-bladder disease, 8 duodenal ulcer and 7 carcinoma of the stomach).

In the series of Benedict and Gillespie[3] 14 had gall-bladder disease, and 42 had gastroduodenal ulcers confirmed by radiologic examination (others had conditions like duodenal diverticula, listed by some authors as possible sources of stimuli but we hesitate to blame such lesions). It seems possible that such a stimulation enlarges and makes permanent an existing hernia and even initiates the development of a hernia and thereby allows abnormal reflux of gastric juice. The evidence on this point is not conclusive, but we believe that reflux stimulation is a possible factor not only in the manner described but also, perhaps, through stimulation of ectopic mucosa or some other means, by making the mucosa more vulnerable just as a duodenal ulcer may become active after disease of the gall bladder.

Coexistence of Gastroduodenal Ulcers and Stenosis of the Esophagus

References on the combination of stenosis of the esophagus with peptic ulceration of the stomach and duodenum are summarized in Table 1. The great majority of such ulcers were in the duodenum—

TABLE 1. *Reports on the Association of Gastroduodenal Ulceration with Esophageal Stenosis.*

YEAR	AUTHOR	NO. OF PATIENTS	NO. OF GASTRODUODENAL ULCERS
1929	Jackson[46]	3	3
1931	Vinson[1]	40	2
1935	Winkelstein[9]	5	3
1938	Benedict & Daland[12]	1	1
1939	Klein & Hochbaum[47]	1	1
1942	Larson et al.[48]	1	1
1946	Benedict[25]	44	15
1948	Benedict & Sweet[2]	60	20
1949	Wangensteen & Leven[49]	6	4
1951	Wilson[5]	22	10
1952	Deaver & McAlpine[50]	1	1
1952	Friedberg & Clayton[51]	6	6
1953	Winkelstein et al.[51]	20	15
1953	Benedict & Gillespie[3]	100	42

Vinson's[1] report merely mentioned the incidental occurrence of duodenal ulcers. This table does not include the reports of authors who do not state how many of their patients had actual stenosis of the esophagus, nor does it include reports on the coexistence of ulcers of the esophagus and duodenum without narrowing. Several other authors (Allison[15] and Olsen and Harrington[16]) refer to the frequency of duodenal ulceration in this condition.

This relation may be interpreted in two ways: either the "ulcer diathesis" is a prerequisite of the development of esophageal stenosis or it is merely an aggravating factor. The incidence of duodenal ulcers is certainly much higher in this group than in the general population, but over half the patients had no radiologic evidence of ulceration and no histories suggestive of such trouble. Another argument against an inevitable association with the ulcer diathesis is that in 6 patients without evidence of duodenal ulcers esophageal stenosis developed postoperatively.

Thus, it seems that the ulcer diathesis greatly predisposes to the development of esophageal stenosis by virtue of the increased secretion of gastric juice and greater liability to gastric reflux even in the absence of pyloric stenosis. It may also be that the ulcer patient has changes in the mucosa of the lower esophagus that make it less resistant to acid-peptic action. But, although this question cannot be settled on the available evidence, it seems that peptic stenosis of the esophagus can occur in the absence of the ulcer diathesis.

Significance of Esophagitis and Esophageal Ulceration

The ulceration of the esophagus in cases of benign stenosis or related conditions has been described as "peptic" by many authors.[4,9,15,19,37,39,40,52,53] Stewart and Hartfall[54] showed the histology of ulcers in the esophagus to be the same as that of ulcers in the stomach and duodenum. Winkelstein,[9] describing 5 cases of "peptic esophagitis," likened this to the duodenitis and antrum gastritis in ulcers of those areas, and thought that gastric juice injured this vulnerable mucosa. Barrett[18] stated that a careful distinction must be made between gastric and esophageal ulcers, for what has often previously been described as "peptic ulcer of the esophagus" is, in reality, a gastric ulcer in a thoracic stomach. Allison[32] believed that regurgitation of gastric juice produced first inflammation of the esophagus and then ulceration, which he described as peptic, and he regarded these as merely stages of the same disease.

Lindau and Wulff[8] refer to Buechner's work showing that fibrinoid necrosis at the base of an ulcer was evidence of acid action, but they considered the site of the lesion—esophagus, duodenum, jejunum and Meckel's diverticulum (that is, areas where gastric juice might occur)—stronger proof of the peptic origin. It would indeed clarify the field if fibrinoid necrosis were reported in all specimens of esophagus when there had been evidence of marked regurgitation or excessive ectopic mucosa, for peptic esophagitis would thus be distinguished from other forms. This, however, is not so, and most authors use the term peptic without definition, generally implying an etiologic hypothesis rather than a pathological connotation. Winkelstein et al.[51] believe, however, that histologic examination of the inflamed mucosa betrays its peptic origin.

All the patients in the series of Benedict and Gillespie[3] showed inflammation of the lower esophagus on direct examination, and all biopsy specimens gave evidence of acute or chronic inflammation or both. Except in 1 case these did not demonstrate a peptic origin (if one insists on proof by fibrinoid necrosis). Forty patients had radiologic evidence of ulceration, 15 being proved at operation, and 2, which had not been shown by barium examination, were found at operation. The 20 operation specimens showed acute or chronic inflammation, or both, in all cases and ulceration in 17 cases, which varied from mucosal erosions to penetrating ulcers. In 6 cases the pathologist reported the ulcers to be "peptic."

From a review of some of the literature on the subject it seems that, although fibrinoid necrosis is proof of acid activity, its presence is not a *sine qua non* for the hypothesis of peptic activity. The ulcer may be quiescent, and in that case fibrinoid necrosis will be absent. It is also difficult to see why all acute ulcers of the lower esophagus do not show this change as a result of the normal degree of gastric-juice regurgitation. We believe, like Allison,[15] that gastric juice produces inflammation that may proceed to ulceration and fibrosis. But in some cases, as in 3 described above, inflammation occurs and progresses to stenosis without apparent ulcer formation.

Other Factors

Surgical operations. Although many writers refer to excessive vomiting as a predisposing cause, only a few (for example, Vinson and Butt[11] and Olsen and Harrington[16]) have spoken of operations preceding esophagitis.

Gastric-suction tubes. Several authors have laid the blame to gastric-suction tubes.[3,4,11,53] A tube was used in 5 of the cases described by Benedict and Gillespie[3] after operation and in another during medical treatment of a duodenal ulcer. If this is a factor in the development of esophagitis it may be by trauma to the mucous membrane, which is thereby made more vulnerable, or else the partial straightening of the lower end of the esophagus (whose closing is partly dependent on kinking) may facilitate incompetence. The reason, however, may be more simple in that patients who require prolonged intubation are generally those who are likely to vomit readily.

Alcoholism. Alcoholism has been considered a factor,[2,5,17,19] and 7 of the patients in the series of Benedict and Gillespie[3] were known to be heavy drinkers. Although it is easy to believe that alcohol may damage the esophageal mucosa it is quite likely that vomiting from gastritis is more important.

Other Theories of the Cause of Benign Stenosis

If peptic activity is not the answer, what is the cause? We have only been able to trace a few suggestions in the literature. Jackson,[46] in 1929, stated that he considered focal infection to be the most important factor in causing peptic ulcer of the esophagus, and Guisez[56] observed that he believed stricture developed as a result of segmental spasm, with retention of secretion followed by inflammation that proceeded to fibrosis.

Infection foci are not so popular now as explanations of distant lesions, and there does not appear to be much evidence to support this thesis. As far as spasm is concerned, there is no doubt that it is often severe in cases of peptic stenosis, but it is unlikely to be the cause of the condition, since cases of achalasia

show relatively little or no inflammation above the cardia.

The mechanism of the cardiac sphincter, the anatomy of the region and its radiologic manifestation are complex and have been discussed by many authors.[19,54,57-60] Here is a region that, by virtue of the angulation of the esophagus and the fact that it is normally kept closed, is liable to trauma and has been designed primarily to prevent anything more than temporary gastric reflux while allowing food to enter the stomach at will.

Treatment

Evaluation of any form of treatment must take into account the erratic course of the disease before irreversible fibrosis occurs — a course as irregular as that of duodenal ulcer. Spasm superimposed on organic changes and often precipitated by emotional stimuli account for the acute exacerbations, and, presumably, edema has a similar effect.

Bouginage

Bouginage is the most widely used treatment, and most authors describe good results[2,6,16,48,61-63] although Allison et al.[13] believed that no patient was completely cured. Few authors give details, but Adams and Hoover[61] reported that all of 14 patients given peroral bouginage were "greatly improved" although 2 had a return of symptoms after being well for five and seven years respectively. Olsen and Harrington[16] performed dilatation every few weeks and then once every six months in 145 patients, some of whom required twenty to thirty dilatations spread over "a period of years." Benedict and Sweet[2] considered the results of bouginage good in 23 cases, fair in 11 and poor in 5 (5 were not followed).

Wilson[5] described good results with conservative treatment in 3 cases with a follow-up period of one and one-half, four and seven years and poor results in 6 cases, 2 being alive after two and seven years respectively, 3 having intermittent symptoms and dying of intercurrent disease, malnutrition probably being contributory, and 1 dying from mediastinitis after esophagoscopy.

Resection and Esophagogastric Anastomosis or Plastic Operations

The procedure and results of this operation have been described by Sweet.[64,65] Of 26 patients suffering from inflammatory stricture of the esophagus, 20 were treated by resection and esophagogastric anastomosis, and 6 by plastic operation (longitudinal incision and transverse closure). One died after operation, and, of the 25 survivors, the results were excellent in 18, good in 6 and fair in 1. Wilson,[5] summarizing the literature and including Sweet's cases, found 34 resections and esophagogastric anastomoses for stenosing peptic esophagitis with an operative mortality of 9 per cent and good results in 90 per cent. He added 1 patient of his own who had the same operation and who was symptom free until his death ten months later from alcoholism, autopsy showing no esophagitis.

There have been several objections to the operation. Allison,[32] reviewing the treatment of benign stenosis, considered esophagogastric anastomosis theoretically unjustifiable because it caused a return to the previous causative condition — that is, a portion of the stomach was lying in the thorax and so reflux of gastric juice into the esophagus could occur. He postulated[32] and later reported[13] the occurrence of peptic esophagitis after such operations for various malignant and benign conditions. Barrett and Franklin[66] found that, of 29 patients treated for cardiospasm, 19 by means of a resection and esophagogastric anastomosis and 6 by cardioplasty, only 4 were subsequently free of esophagitis. Ripley, Olsen and Kirklin[23] observed that of 65 patients who had esophagogastric anastomosis or cardioplasty 28 had definite evidence and 12 presumptive evidence of peptic esophagitis or formation of a stricture. Loe[57] wrote a valuable editorial on the subject of the esophagogastric-valve mechanism, stressing the importance of its preservation. In the experiments of Ripley et al.[67] ulceration and stricture formation followed esophagogastric anastomosis.

Sweet[68] recently reviewed 50 operations for esophageal stenosis in which he did 1 limited and 33 extensive esophagectomies, 8 extensive gastrectomies and 8 esophagoplasties. There were 4 hospital (postoperative) deaths, all among patients subjected to one type of extensive resection. One of these resulted from pulmonary embolism complicating a coronary occlusion. The second was due to pulmonary insufficiency in an elderly man with widespread bilateral fibrotic pulmonary tuberculosis with cavitation at both apexes. The third resulted from the aspiration of gastric contents in an elderly, feeble woman with a limited pulmonary reserve. The fourth, which was definitely related to the technical aspects of the procedure, resulted from perforation of an ulceration at a point where a portion of the stomach had become incarcerated from herniation through the opening made in the diaphragm at the time of operation. Of the 35 patients who were followed, the results were excellent in 20, good in 6 and what might be termed relatively poor in only 3. Recurrent esophagitis was known to have occurred in 3 of the 35 patients followed. The evidence presented bears out the impression that surgical measures should never be deferred in any case of ulcer or stricture of the esophagus in which there is a history of bleeding, obstruction unsuccessfully treated by bouginage, intractable pain or evidence of perforation. If the operative procedure is carefully chosen to suit the conditions encountered and the age and physical status of the patient, satisfactory clinical result can be anticipated in at least 90 per cent of the cases. A diagnosis

of recurrent esophagitis after operation can be established only on the basis of roentgenologic and esophagoscopic examination, but conclusive proof of the diagnosis depends on the use of the esophagoscope.

Resection and Esophagojejunostomy

Allison[32] reported 1 case in 1946 and 5 in 1948[15] in which partial resection of the esophagus and esophagojejunostomy were performed. In 1951 Allison[4] said that all of 15 patients with chronic esophageal ulcer and stenosis who had had this operation were alive and well, and he considered it to be the procedure of choice. Tanner[69] agreed with this opinion. In theory esophagojejunostomy is certainly preferable to esophagogastrostomy, for it abolishes reflux of gastric juice. It is technically more difficult, however, and at present there appear to be no adequate figures to prove its superiority to esophagogastrostomy.

Although it is unlikely that intestinal juice is as harmful to esophageal mucosa as gastric juice, there is some evidence that it can be injurious, as shown by the occasional development of stenosis after resection of the stomach and esophagojejunostomy for carcinoma involving the cardia.[61] At least 4 such cases have been seen in the Endoscopy Clinic of the Massachusetts General Hospital in recent years, but it is possible, of course, that the stenosis was due to other mechanisms.

Vagotomy

Vagotomy done alone or combined with other procedures to reduce acidity has been rejected by Allison[15] on the grounds that it is inadequate. Ripley et al.,[23] discussing this point, refer to the belief that vagotomy does not influence the gastric or intestinal phase of gastric secretion. Although vagotomy is of some theoretical advantage its practical value is unproved. It does, however, seem likely that its routine employment in cases treated by resection and esophagogastrostomy is helpful in reducing gastric secretion and so minimizing the harmful effects of the almost inevitable gastric reflux.

In the series of Benedict and Gillespie[3] vagotomy and posterior gastroenterostomy were performed in 1 case for a duodenal ulcer, but, instead of preventing stenosis, this operation was followed by the development of esophageal stenosis.

Gastric Resection

Wangensteen and Leven[49] reported that all of 6 patients who had esophagitis or a stricture were relieved after gastric resection. They observed that a patient who had had about 100 dilatations over a period of four years did not require any further dilatation after gastric resection. This man was followed for five years with no recurrence; another was also followed for five years after operation, a third was followed for two years, and a fourth for eleven months. Tanner[69] said that he had treated 6 patients in this manner but that it was too early to recommend the operation for other cases. Wilson[5] described 2 patients, 1 of whom died whereas the other remained well for twenty-one months after operation. Van Aken,[70] however, reported the development of a stricture after gastric resection. The results presented by Wangensteen and Leven[49] were so good that this appeared a profitable line to investigate, but in 5 patients in the series of Benedict and Gillespie[3] gastric resection had been performed for duodenal ulcer before the development of dysphagia and so in these cases it was of no obvious prophylactic value. In 1 case gastrectomy was done after the development of peptic stenosis but was without apparent effect on the dysphagia. Thus, although we consider the operation theoretically justified so far as it reduces the volume of gastric secretion there is inadequate evidence of its prophylactic or curative value.

Repair of Hiatus Hernia

Allison[4] advocated the repair of hiatus hernias on the grounds that this deformity caused reflux esophagitis, and he reported the results of repair in 33 of 73 patients who had esophagitis but no stenosis. In 30 cases there was relief of symptoms and a normal radiologic appearance. One patient died from coronary thrombosis; 1 had a recurrence of the hernia, and 1 had postoperative esophagitis and an incompetent cardia without "anatomic" recurrence of the hernia. Although the length of follow-up period is not given, these results and the theoretical basis for the operation strongly suggest the advisability of repair of hernias if serious symptoms exist before the development of stenosis. It is not known, of course, how many of these cases would have progressed to stenosis. Wilson[5] reported an unfavorable result in 1 case after repair of a hernia, but this operation followed development of stenosis. In the series of Benedict and Gillespie[3] 5 patients had repair of a hiatus hernia without other surgery except that 1 operation was combined with a cardioplasty. Of these cases the hernia recurred in 3; in another, repair was done because of bleeding, but the peptic stenosis had previously been treated satisfactorily by bouginage. It is thus not possible to draw conclusions, but it is reasonable to say that hiatus hernia is one of the etiologic factors since 85 per cent of the present cases had such a hernia. If hiatus hernia exists alone and causes symptoms that are not relieved by posture, diet and proper medical measures operation is clearly indicated, regardless of the possible development of stenosis.

Conclusions

Peptic stenosis of the esophagus is due to abnormally prolonged contact of gastric juice with the region above the cardia. Peptic stenosis can occur in a normal person, but it more probably occurs in patients with the ulcer diathesis.

Gastric juice occurs in the lower esophagus to an abnormal extent as the result of the following factors: esophageal hiatus hernia of the sliding type; and excessive vomiting or regurgitation from relaxation of the cardia.

The peptic-ulcer diathesis is an important contributory cause, for it means that there is generally an excessive amount of gastric juice and the patient often has indigestion with regurgitation or vomiting even in the absence of pyloric stenosis.

Esophagitis is present in all cases, and almost half the patients have evidence of ulceration. Ulceration, which is generally superficial but may be deep and penetrating, represents a more severe form of the disease. Histologic examination may provide evidence of peptic activity, but its absence does not rule out the diagnosis since the ulcer may have healed with considerable scarring and contraction of the esophagus.

There appears to be no adequate explanation in the literature to account for this type of benign stenosis of the esophagus.

In view of these findings, it is desirable to repair hiatus hernias that are causing symptoms and do not respond to other measures. Although the importance of hiatus hernia appears real there is at present inadequate evidence to prove the value of repair operations as a prophylactic measure.

In theory gastrectomy for gastroduodenal ulcers ought to be of value in preventing the development of peptic stenosis of the esophagus but the present evidence does not support this thesis.

Avoidance of excessive vomiting, if this goal can be achieved, is obviously desirable, as is avoidance of any factor that facilitates regurgitation such as unnecessary recumbency.

Before treatment is begun, it is essential in view of the resemblance to malignant lesions to make certain of this diagnosis by means of radiography, esophagoscopy and biopsies, repeated if necessary.

Bouginage, after the swallowing of a thread, is satisfactory in most cases. It is generally not possible to ascertain beforehand how many treatments will be required, and results bear no obvious relation to such factors as the length of history, the degree of dysphagia and the degree of stenosis as found at esophagoscopy. Bouginage should be combined with dietetic treatment, antispasmodics and antacids and measures to prevent the occurrence of reflux such as the repair of a hiatus hernia if it is causing serious symptoms.

Surgical treatment is necessary in cases of excessive bleeding and failure to respond to bouginage and when there is risk that an ulcer will perforate. The results of resection with esophagogastric anastomosis are good in most patients who survive the operation. Although esophagojejunostomy seems theoretically a preferable operation it is more formidable, and there is, as yet, insufficient information on this subject.

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MEDICAL INTELLIGENCE

LATERAL CERVICAL MYELOGRAPHY

WARREN R. SISSON, JR., M.D.*

BOSTON

EVER since Brain and his co-workers,[1] called attention to the condition described under the name of spondylosis cervicalis, this department has felt the need for a method of taking lateral cervical myelograms that gives a consistently good lateral view of the boundaries and contents of the cervical spinal canal, that is relatively easy to carry out and that reduces to a minimum the chance of getting the Pantopaque above the foramen magnum. The last requirement is believed to be particularly important because of experiences with several cases in which the Pantopaque, which had escaped from the control of the operator, lodged in the curve of the occiput and defied removal by any means, as well as because of the death of a patient in whom the Pantopaque had left the occiput, migrated upward into the aqueduct, lodged there and caused death from obstructive hydrocephalus, the condition having been verified at post-mortem examination.

Earlier attempts at lateral cervical myelography had consistently failed, basically because the operator was afraid of losing control of the dye. The lateral views were not lateral; the dye had not extended high enough; it had broken into bubbles and was nondiagnostic; or everything that had been considered essential to see in a cervical myelogram up to that time could be seen as well or better in the posteroanterior views.

A diagnosis of spondylosis cervicalis on which therapy is to be based is impossible on no better evidence than that discussed above. Good lateral views of the cervical spinal canal are essential. It is also necessary to have a method that is not too complicated to use and in which the ascent of the Pantopaque can be controlled at all times by the operator. The following technic meets these requirements and has given satisfaction for a year in the performance of 10 lateral cervical myelograms. Of course, at the time of the examination posteroanterior views of the filled cervical or any other level of the spinal canal are also included. If possible, and this depends on the ease of performance, stereoscopic lateral views are taken. This can only be done occasionally, however.

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The usual lumbar puncture with a Queckenstedt test for cerebrospinal-fluid obstruction done with the neck in neutral position as well as in flexion and extension, if not contraindicated, is performed with the patient on his side on the tilting x-ray table. A 10-cc. specimen of cerebrospinal fluid is collected for appropriate analysis, and 6 cc. of Pantopaque is slowly injected into the lumbar subarachnoid space, after which the lumbar puncture needle is withdrawn. In this, as in all such examinations, it is important to have the patient relaxed, and indeed in this particular test it is essential. A *painless* lumbar puncture[2] must be done — when necessary, more local anesthetic is added at the time of the withdrawal of the Pantopaque if the patient complains at all. At least 10 cc. of procaine — 1 or 2 per cent — is the minimum that will assure freedom from pain and hence co-operation on the part of and safety for the patient.

The table is kept horizontal during the injection of the Pantopaque, and after that has been completed the patient is made comfortable on the table on his stomach, and his shoulders are brought up firmly against shoulder supports that are tightly attached to the table to prevent slipping. The patient's head and neck are then somewhat hyperextended to prevent overflow during manipulation of the Pantopaque through the foramen magnum into the posterior fossa of the cranial cavity. This hyperextension is accomplished if the patient places his fists beneath the chin or if the physician places a suitable pad beneath the chin.

After the proper position of the patient has been attained, his head, neck and hands have been fixed and he has been told not to move, the fluoroscope is adjusted, and by slow tilting of the table head downward the dye is gradually brought up the spinal subarachnoid space until it reaches the thoracocervical junction. At the point of the lumbothoracic junction there is a definite hump, over which the dye has to be moved with care to prevent the operator's losing control of it after it has entered the more downward-sloping upper thoracocervical subarachnoid space. It is for this reason that 6 cc. rather than a smaller amount of the dye is used in this test. Such a quantity renders it unnecessary and undesirable to get *all* the dye over this hump, the lesser amount that enters the cervical subarachnoid space at the first shift from the thoracic space being sufficient for all purposes. The chance of introducing some of the first contingent of dye from the cervical spaces into the cranial cavity by endeavoring to introduce a second contingent into the cervical space is thus largely eliminated. The greater part of the dye should be puddled in the lower part of the cervical subarachnoid space, above the cervicothoracic hump and well below the foramen magnum after this procedure.

The head of the table is then slowly raised until it is horizontal. Simultaneously, as the table starts to move, the patient removes his fists from beneath his chin (or the operator removes the sandbag), the head being grasped and held in the operator's hands in its original hyperextended position and under the full control of the operator. As the head of the x-ray table continues to rise the operator simultaneously and slowly flexes the patient's neck and head and thus moves the mass of dye slowly up the cervical subarachnoid space and provides a posteroanterior view of the contents of the spinal canal. This aspect of the canal and its contained dye can be recorded permanently by films of it taken as often as one considers suitable. Since the dye is well controlled there is no haste and no reason for the dye to enter the cranial cavity.

Preparation is then made to take the lateral views. The ceiling light is put on. The observer retains his grasp and control of the patient's head and its position with one hand, leaving the other free. The patient is warned neither to move nor to cough. The x-ray technician carefully removes the shoulder supports and places a cassette standing upright against each side of the neck, where henceforth it is held in place by the free hand of the observer, after which the necessary films are exposed, removed and developed for checking (Fig. 1).

While this is being done the patient is helped into the sitting position, thus causing the dye to drop out

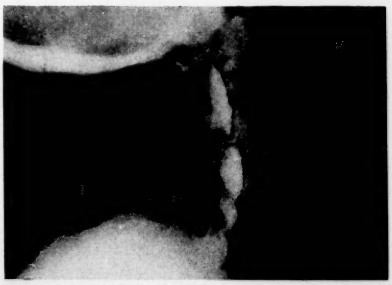

FIGURE 1. *Lateral Cervical Myelogram in a Patient with Cervical Spondylosis.*

of the cervical and into the sacral cul-de-sac. The patient can now lie down with the head slightly elevated above the pelvis on the tilting x-ray table to await the verdict on the films. If they prove unsatisfactory the whole procedure may be repeated with due care to correct the deficiencies apparent in the first set. If the films are adequate, more procaine is injected locally in the lumbar region, a lumbar puncture performed, a syringe attached to the hub of the needle in place of the withdrawn stilette, and the ceiling light is put out. Then, with the fluoroscope as a guide, the examiner, by adjusting the tilt of the

table, brings the mass of dye into contact with the open end of the needle in the lumbar subarachnoid space. With this accomplished the dye is withdrawn under fluoroscopic control with the syringe on the hub of the needle.

If care is taken to prevent the entrance of any air into the subarachnoid space and to refrain from reducing the intracranial pressure more than 10 mm. of water with the patient horizontal, virtually all headaches after lumbar puncture will be eliminated.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40151

PRESENTATION OF CASE

A nine-month-old girl was admitted to the hospital because of cough and difficult breathing.

The onset of these symptoms was fairly sudden at the age of a month. During the night the mother heard the patient wheezing, and the next morning paroxysms of coughing occurred. There were several episodes of cyanosis, and "heavy breathing" became severe. These symptoms remained for ten days and then gradually lessened, but cough and difficult breathing persisted with exacerbations and remissions. At no time was there nasal discharge or fever. The mother did not recall any foreign body that could have been aspirated. At six months of age, when the patient was taken for a routine checkup, a roentgenogram of the chest revealed "lung cysts." The physician advised re-examination in six months to see if the cysts would regress spontaneously, but because of the persisting symptoms the patient was brought to the hospital.

Delivery had been normal and at full term. The birth weight was 7 pounds. No previous illness had been noted.

Physical examination disclosed a well developed, well nourished child of good size for her age. She could sit alone. She appeared chronically ill, and had moderate respiratory distress with suprasternal, infrasternal and subcostal inspiratory retraction. There was prominence of the right side of the chest anteriorly and distention and pulsation of the neck veins. The position of the trachea could not be determined. There was hyper-resonance throughout both lung areas; breath sounds were diminished, especially over the right upper part of the chest anteriorly. The heart beat was best felt over the fifth intercostal space outside the left midclavicular line. There was a loud Grade 2 to 3 blowing apical systolic murmur transmitted to the back. Heart sounds were very faint over the heart base. There was no clubbing of the fingers or cyanosis. No other abnormality was noted.

The temperature was 99°F., the pulse 134, and the respirations 30.

Urinalysis was negative. Examination of the blood showed a hemoglobin of 13.6 gm. per 100 cc. and a white-cell count of 10,700. Fluoroscopic study demonstrated marked deviation of the heart and mediastinal structures to the left, owing to a huge cystic dilatation of part of the right lung (Fig. 1 and 2). The right lung was herniated well beyond the midline and extended primarily anteriorly. Some aerated right lung was seen in the lower chest and apex. The cystic area appeared to have septums within it. The left lung was also emphysematous but diffusely aerated and without evidence of cystic dilatation. The configuration of the heart was distorted, with some uplifting of its apex. There was no pleural fluid. There

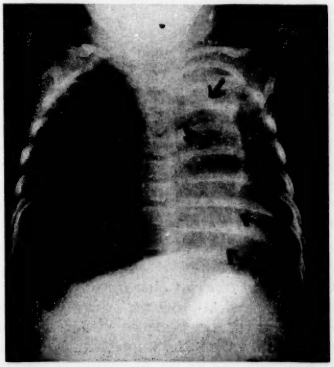

FIGURE 1. *Posteroanterior View of the Chest. Arrows overlying the left half of the thorax indicate the extent of herniation of the cyst. The arrow near the spine points to the fleck of calcification opposite the fifth thoracic vertebra.*

was a 5-mm. fleck of calcific density at the level of the fifth dorsal vertebra about 2.5 cm. anterior and to the left of this vertebra. The patient swallowed barium normally, and the esophagus was normal and without evidence of vascular indentation. On the third hospital day an operation was performed.

Differential Diagnosis

Dr. J. Gordon Scannell*: This seems to be a fairly straightforward and fascinating case in which I am sure that I shall learn a good deal more from the pathologist's verdict than anyone will learn from my discussion.

In brief we have an otherwise healthy infant with striking emphysematous changes in the right lung.

Figure 2. *Lateral View of the Chest. Arrows indicate the posterior extension of the cyst.*

and the protocol hints of changes on the other side in both the physical and the x-ray examination. There is no particular evidence of concomitant infection, nor do I have the impression that infection played a serious role in the beginning of the illness. It should be re-emphasized that an acute pneumonitis or pneumonic process in an infant can suddenly produce marked emphysematous changes that are quite reversible though they occasionally go on to more serious complications; the history does not suggest such a train of events.

May we see the films, Dr. Hanelin, which I have had the advantage or the disadvantage of seeing before I came here?

Dr. Joseph Hanelin: There is a huge, air-filled cyst of the right lung that extends across the midline anteriorly into the left half of the thorax (Fig. 1). There is a suggestion of some trabeculation through it, or else we may be looking at a portion of the cyst wall that is irregular since it lies against the atelectatic remaining right lung. There is some evidence of aerated lung toward the apex of the right side of the chest posteriorly and extending downward to the base. The mediastinal structures are displaced markedly toward the left. The left lung is normal, and the heart is not remarkable except for the altered position.

Dr. Scannell: Do you see anything that resembles a fissure?

Dr. Hanelin: In the lateral projection (Fig. 2) there is a suggestion of a fissure, and a linear density traverses the thoracic area that conceivably may be the lower end of the major septum on the right. The small fleck of calcification that was referred to in the protocol is observed slightly to the left of the fifth thoracic vertebra.

Dr. Scannell: Can this be regarded as a "red herring"?

Dr. Hanelin: In this location this type of calcification has been described in the obliterated ductus arteriosus.

Dr. Scannell: That is indeed superscience. I do not wish to become involved in semantics with Dr. Hanelin, or I should take exception to the term "huge, air-filled cyst of the right lung" because such a cyst, if present, would be the diagnosis and I could sit down.

We have clear evidence that the right lung had expanded beyond its normal limits at the expense of the left lung. It is not quite clear from these films whether the expansion was confined to one lobe or involved the whole lung. It appears to be more noticeable in the upper anterior part of the chest and through the anterior mediastinum, which is the line of least resistance. This suggests to me that the process may well have been primary in the right upper or the right middle lobe or both. This enlargement does not appear to be cystic in the ordinary sense of the word; it does not have a clearly defined contour, nor does it contain fluid.

Congenital cysts of the lung do occur, often communicate with open bronchi and often contain air with or without fluid. They also may encroach on the other lung, on the remainder of the lung in the same pleural space or on the other thoracic contents. It is my impression, however, that when they do this they have a more clearly defined wall than we see here. They are prone to infection, but that no infection was present in the case under discussion has no bearing one way or the other on the diagnosis. I do not think that the x-ray findings exclude cystic disease, but what I mean by congenital cystic disease of the lung does not have this x-ray appearance.

I should prefer to consider relatively localized emphysema associated with some valvelike obstruction to a lobar or to a major bronchus. This abnormality, as a disease, has been well known for some time. The picture was well presented at the last Thoracic Surgical Meeting by Sloan[1] of the University of Michigan.

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The cause of the bronchial obstruction I can only surmise. Certainly, a foreign body with consequent inflammation could obstruct a bronchus. The patient's mother may not have recalled any specific object that was inhaled, but we are all well aware of the indiscriminate attitude of babies toward foreign bodies. Furthermore, the relatively abrupt onset of symptoms and the mysterious fleck of calcium suggest this diagnosis. I cannot exclude it on the basis of the history or the findings, but I think it is unlikely on the basis of the probable localization of the process in the upper lobe, the absence of more evidence of infection and more difficulty, and the vague nature of this fleck of calcium. I doubt if I should have bronchoscoped this patient because I think the respiratory effort entailed might have proved very embarrassing indeed.

I shall only mention the possibility of a tumor because it is so rare.

I think probably the answer lies in some architectural abnormality in the bronchial wall. The absence of bronchial cartilage and cartilaginous rings may produce a flattened, soft bronchus, which interferes with normal ventilation, usually by hindering expiration. If this occurs in a lobar bronchus emphysema develops distal to the obstruction; the emphysema may be confined to that lobe or to two lobes between which the fissure is not complete. This incompleteness is likely to be present between the right upper and middle lobes. The degree of emphysematous spread from the obstruction, I suppose, depends on the collateral air drift throughout the interalveolar pores. It has been suggested that excessively vigorous resuscitation of the newborn infant may produce emphysema. We are only told that this patient's delivery was normal. We are given no facts at all regarding forceful efforts at resuscitation.

In summary, therefore, it seems likely to me that this patient had a congenital defect of the bronchial tree and the pulmonary architecture and that this was manifested in obstruction and emphysema of one lobe particularly although diffuse changes may have existed throughout the remainder of the lung. These changes, I think, occurred in the lobe that in this patient had the poorest bronchus — the right upper, with or without the middle lobe. I think that the prognosis has to be guarded but that it is not by any means predictably bad.

DR. BENJAMIN CASTLEMAN: Would you have operated on the child?

DR. SCANNELL: Yes—on the basis that this was known to be present for three months, that it was progressing and seemed to be symptomatic.

DR. CASTLEMAN: Dr. Nathan B. Talbot followed this patient and asked Dr. Soutter to see her.

DR. LAMAR SOUTTER: This patient presented a difficult problem in therapy largely because the exact diagnosis before operation was uncertain. She had been studied five months previously in another hospital, where the cyst was considered to be a simple one that might well regress without treatment. Her physician became disturbed when it did not and requested a re-evaluation of the problem. In five months the chest had enlarged somewhat, but the cyst had grown proportionately, producing a serious degree of pulmonary compression. Furthermore, the patient was beginning to have signs of malnutrition; the chest wall had become markedly deformed. She became cyanotic on deglutition, and she had had several bouts of respiratory infection. The presence of the cyst had made her existence precarious. When she entered this hospital her condition provoked much discussion on the Children's Medical Service because a good deal has been written to prove that the simple intrathoracic cysts appearing in the first year of life usually disappear spontaneously. As Dr. Scannell has so carefully pointed out, however, this was not the ordinary bronchogenic cyst but resembled bullous emphysema, which usually does not regress. Furthermore, it was much larger than most of the reported cysts and more embarrassing to the patient. Our process of reasoning was exactly the same as his. We discussed the possibility that a foreign body had been the etiologic factor, but could obtain no such history from the mother. This, of course, did not exclude the possibility. In the face of serious respiratory embarrassment in a small child a diagnostic bronchoscopy would have been very hazardous. Bronchography would also have been dangerous. Continued observation in the hospital, which is the only place where such a course may be carried out safely if a pulmonary cyst is very large, seemed to be fruitless. We decided to remove the cystic area as the safest procedure for the patient. We believed preoperatively that the cystic area arose in the middle or upper lobe of the right lung.

CLINICAL DIAGNOSIS

Cyst of lung.

DR. J. GORDON SCANNELL'S DIAGNOSES

Pulmonary emphysema, localized.
Congenital defect of bronchial tree.

ANATOMICAL DIAGNOSIS

Pulmonary emphysema, with pneumatocele, right middle lobe.

PATHOLOGICAL DISCUSSION

DR. SOUTTER: At operation the cystic area occupied the anterior portion of the chest. It represented an emphysematous and cystic expansion of the lateral segment of the middle lobe. The medial segment was normal but had expanded into the apex of the chest and assumed the contour of an upper lobe. The upper lobe was small and atelectatic and lay behind

it. There were extensive adhesions between the parietal and the visceral pleura, indicative of previous inflammation. After we had removed the cystic area the remaining bronchus felt perfectly normal, but there were sufficient inflammatory changes around it to prevent us from either confirming or denying Dr. Scannell's suggestion of an abnormality of the bronchus. At the end of the operation the lung re-expanded well, and the patient had an uneventful convalescence.

DR. CASTLEMAN: The slide of the cyst (Fig. 3) confirms Dr. Scannell's and Dr. Soutter's impression. The specimen was made up of large emphysematous alveoli, some of which had apparently resulted in the huge cystic formation. This was certainly not the

FIGURE 3. *Photomicrograph (x 30).*
The dilated emphysematous blebs are filled with hemorrhage, apparently the result of operative manipulation.

appearance that one sees in the true cyst of the lung. Another interesting finding was hemosiderin in monocytes in the wall of this cyst, which indicated that perhaps at some time in the past there had been hemorrhage as a result of a rupture of some of these alveolar walls.

A great deal has been written within the past twenty years questioning whether any cysts of the lung are congenital. Many physicians now believe, as we do here, that if there are congenital cysts of the lung they are extremely rare. Most physicians believe that even the cysts in children are acquired rather than congenital. In a series of over 6000 infants Potter,[2] of Chicago, who has seen more infants' lungs than any other person in the world, has found only 2 cases of congenital pulmonary cysts, both of which were in stillborn infants. We have never seen a cyst in a stillborn or a newborn infant. Most of the cysts that pathologists have called congenital have been found with bronchial epithelial lining, but that is not enough evidence for us to assume that they are congenital in origin. Such a cyst certainly may be acquired and may be lined by proliferation of bronchial epithelium. I think in this particular case there was no evidence of that, however, and I believe the cyst was a blown-up emphysematous bleb.

The other point that was emphasized by both Dr. Scannell and Dr. Soutter is that most of the cystic spaces in the lung of a child eventually disappear. A recent article[3] reported the formation of cysts as large as this as a result of pneumonia with destruction of tissue that produced a pneumatocele. This disappeared after several months. It is essential to realize that all such patients need not be operated on.

DR. FARAHE MALOOF: What has happened to the child?

DR. HANELIN: Eight days later there was a remarkable change in the chest: the mediastinum was almost in the midline; the right lung had expanded well and there was only a little residual pleural fluid. I understand that the child has done very well.

DR. SOUTTER: When I saw her a few days ago (six weeks after operation) she was fine.

DR. SCANNELL: Did Dr. Soutter do a biopsy of the upper lobe to see if there were early changes of emphysema in the remainder of the lung?

DR. SOUTTER: No; the upper lobe was small but normal in texture and appearance. Because of the child's critical condition at the time of operation we decided to do nothing more once the cystic area had been excised.

DR. SCANNELL: This was not a cyst in the ordinary sense, but an emphysematous bulla or bleb, and it would have been interesting to see whether other changes could have been detected as a clue to what might happen in ten, fifteen or twenty years.

DR. CASTLEMAN: One often sees this condition in adults.

DR. SCANNELL: It is frequently seen, and usually, as in this patient, one segment is involved first.

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CASE 40152

Presentation of Case

First admission. A forty-seven-year-old man entered the hospital because of pain in the feet and knees.

For twenty-five years the patient had had painful feet, for which he had worn various types of arch supports. The pain was limited to the metatarsophalangeal joints and occurred almost entirely during periods of weight bearing. A year before entry he noted the onset of stiffness in the knees, associated with some pain, that was worse early in the morning and subsided during the afternoon. The feet and knee symptoms gradually became worse during the week and eased up during the week end when he was able to stay off his feet. The proximal interphalangeal joint of the right fifth finger had also been slightly swollen and stiff. An x-ray film of the feet two months before entry showed narrowing of the metatarsophalangeal joints, thickening and destruction of the adjacent cortical bone, with subchondral absorption, and several radiolucent areas in the heads of the metatarsals. Anomalies of the first distal phalanges of both feet were present. For the week before admission the patient was treated with bed rest, hot baths and aspirin with some improvement.

Two and a half years before admission the patient had had a physical checkup because of a period of anorexia; at that time the basal metabolic rate was said to be normal. There was no history of swelling or pain in the neck, or of thiouracil or thiocyanate ingestion. One sister had "some kind of goiter trouble." He had been born in Canada but had lived in Boston for thirty-one years.

Physical examination revealed a well developed man in no acute distress and except for the joints was negative. He complained of pain in his feet when he had to walk. There was a full range of movement in the ankles and knees, with no localized tenderness or swelling. The proximal interphalangeal joint of the right fifth finger was slightly enlarged and was fixed in partial flexion.

The temperature, pulse and respirations were normal. The blood pressure was 140 systolic, 94 diastolic.

Examination of the blood showed a hemoglobin of 15.3 gm. per 100 cc. and a white-cell count of 13,900, with a normal differential. The erythrocyte sedimentation rate was 0.80 mm. per minute, and the hematocrit 45 per cent. The nonprotein nitrogen was 35 mg., and the serum uric acid 3.9 mg. per 100 cc. The urine had a specific gravity of 1.024 and was normal.

The patient was given physiotherapy and discharged improved after ten days.

Second admission (eighteen months later). During the year before admission he had noted the insidious onset and progression of fatigue, listlessness, mental and physical sluggishness and lack of ambition. During the same period he became sensitive to cold, with a "chilly feeling" at temperatures that his friends found to be comfortable. Six months before admission his friends noted that his face appeared swollen and puffy and that his voice had become deep and hoarse. During the year before admission he gained 16 pounds in weight, most of which allegedly was distributed around his shoulders. His appetite remained good; bowel movements were regular, and the texture of the skin, hair and nails did not seem to change. He had continued to have intermittent attacks of pain and swelling in the feet, knees and wrists; these had been less troublesome in the few months before admission.

Physical examination revealed a man who was very placid, who was physically and mentally sluggish, who spoke with a hoarse voice but who was not complaining of any discomfort. The face was puffy. The skin, hair and nails were normal. The tongue was larger than normal. The thyroid gland, which was diffusely enlarged to one and a half times the normal size, had an irregular, lobulated surface and felt firm and rubbery. It was not tender and was freely movable. The remainder of the physical examination was negative.

The temperature was 97.4°F., the pulse 64, and the respirations 16. The blood pressure was 140 systolic, 100 diastolic.

Examination of the blood showed a hemoglobin of 14.2 gm. per 100 cc. and a white-cell count of 12,600. The sedimentation rate was 48 mm. in 60 minutes. The serum sodium was 133.4 milliequiv., the chloride 98 milliequiv., and the potassium 4.3 milliequiv. per liter; the cholesterol was 532 mg. per 100 cc. The urine was normal. A Congo-red test demonstrated 62 per cent retention in the serum at the end of an hour. The basal metabolic rate was −21 per cent. A forty-eight-hour radioactive iodine uptake was 3 per cent. A glucose tolerance curve showed a blood sugar of 71 mg. per 100 cc. fasting and 123 mg. thirty minutes, 151 mg. one hour and 72 mg. per 100 cc. two hours after ingestion of glucose. A roentgenogram of the chest was normal.

On the ninth day an operation was performed.

Differential Diagnosis

Dr. Farahe Maloof*: This forty-seven-year-old man had two problems: "arthritis," which he may well have had for twenty-five years, and a metabolic disturbance — namely, myxedema. The two conditions were probably unrelated, although there is one diagnosis that could link them together.

The joint manifestations, I believe, can best be explained by the diagnosis of rheumatoid arthritis, which was probably present for twenty-five years. The description of the roentgenograms of the feet is certainly

*Assistant in medicine, Massachusetts General Hospital.

characteristic of rheumatoid arthritis. I cannot logically substantiate any other diagnosis. The radiolucent areas in the bones are usually seen in patients with gout, but can be seen in patients with rheumatoid arthritis.

The second problem, and the reason for the last admission, is fairly obvious. I do not believe that one can make any diagnosis but myxedema of a year's duration. The reason for the anorexia two years before the first hospitalization is not clear to me, nor is the reason for the low basal metabolic rate if anorexia was the only symptom. However, it is possible that the thyroid gland was enlarged at that time. The history contained no reference to swelling or pain in the neck that could have been caused by acute thyroiditis or hemorrhage into a thyroid cyst. I am also told that the patient was not taking two of the many goitrogenic drugs, which are discovered each day. In the first hospitalization the examination was negative except for a slightly elevated diastolic blood pressure and the joints.

He was then given physiotherapy and discharged as improved. I am not told about any medication. Although the diagnosis of myxedema is clear, the etiology is obscure. Was this agnogenic or iatrogenic myxedema? An enlarged thyroid gland in a patient with myxedema is usually due to the ingestion of a goitrogen or to Hashimoto's thyroiditis. Medication given to patients for "arthritis" and known to be antithyroid are butazolidin, cortisone, which will depress the uptake of I^{131} (radioactive iodine) by the thyroid gland, lower the serum protein-bound iodine and produce symptoms of hypothyroidism (there is no evidence that it will produce a goiter or myxedema) and the known antithyroid drugs such as propyl and methyl thiouracil.[1] The logic for the last is not clear to me, for lowering the metabolism of patients with arthritis usually aggravates the joint symptoms. However, I am surprised to note that the joint symptoms were better for two months before the last admission at a time when he was myxedematous. Since patients with primary myxedema[2] and patients with rheumatoid arthritis tend to have lowered adrenal function,[3] it is difficult to rationalize this form of therapy.

The description of the thyroid gland is compatible with Hashimoto's thyroiditis and not with that of a gland that had been under the influence of a goitrogen; such glands are usually larger and softer and may be quite vascular. He had a slight leukocytosis, but I am not told about the differential count in the last admission. The serum sodium and chloride were low, and the cholesterol was high; all are consistent with the diagnosis of primary myxedema.

The Congo-red test was negative. This suggests that with the arthritis and the goiter the physician was wondering about amyloid disease of the thyroid gland. Amyloidosis is said to occur in about 25 per cent of patients with rheumatoid arthritis. I have seen a patient with primary amyloidosis[4] and a large amyloid goiter, but he was not myxedematous. Besides there is little here on which to make a diagnosis of primary amyloidosis though such patients have symptoms simulating arthritis. Another patient had amyloidosis secondary to rheumatoid arthritis; he was euthyroid by all the indexes of thyroid function in spite of a large amyloid goiter.

The basal metabolic rate and the I^{131} uptake are consistent with the diagnosis of myxedema, but are not helpful in telling me the etiology. I do not understand why a gastrointestinal series and a glucose tolerance test were done; however, if aspirin had been given he might have had gastrointestinal symptoms and a positive test for sugar in the urine. I am told that a roentgenogram of the chest was normal. This is a bit surprising, for I should have expected the heart shadow to be enlarged. I have seen it increase in size as early as two months after the development of postoperative myxedema in a twenty-eight-year-old man.

An operation was performed. I find no indication for thyroidectomy, for it is extremely unusual to have carcinomatous infiltration of the thyroid produce myxedema before such a process kills the patient. Rarely, thyroid carcinoma is found in association with thyroiditis. I believe that a needle biopsy of the thyroid gland was performed and that a Hashimoto thyroiditis was found. I cannot rule out an amyloid goiter.

May we see the roentgenograms?

DR. JOSEPH HANELIN: Films of the feet three years before admission demonstrated arthritic changes limited to the metatarsophalangeal joints on either side. Only the first and second metatarsophalangeal joints on the right and the third metatarsophalangeal joint on the left are spared. The involved joints reveal severe reduction in joint spacing, destruction of articular surfaces and cystic changes in the adjoining portions of the bones. Hallux valgus is present on the left, and there are extremely sclerotic changes of the bone margins at this joint. Osteoporosis is relatively mild and more marked on the left about the fourth and fifth metatarsophalangeal joints. The joint changes are characteristic of rheumatoid arthritis.

Chest films, made seven months before admission and also at the time of hospitalization, show the lungs to be clear and moderately emphysematous. The trachea is not displaced or narrowed. No obvious mass is visible within the neck or mediastinum. The heart is not enlarged.

An upper gastrointestinal examination during hospitalization discloses no abnormality except for a small hiatus hernia. The spleen is not enlarged.

DR. JOHN B. STANBURY: Clinically, this patient presented obvious hypothyroidism and in addition had a small, definitely irregular, firm thyroid gland. As I recall, it was a little larger on the left side. In all respects the findings were typical of Hashimoto's thy-

roiditis except that the patient was a male. This disease is not exclusively a disease of females, but by far the majority of our patients are women. Dr. Maloof has thoroughly covered the differential diagnoses. We have never seen cancer destroy the thyroid gland to a point where hypothyroidism has been definite. This patient gave no history of any symptoms suggestive of an acute thyroiditis that might have resulted in hypothyroidism and a scarred gland. Patients with Hashimoto's thyroiditis never have symptoms directly referable to the gland except that they may have pressure symptoms. Patients with nodular goiter almost never present the frank picture of myxedema, and accordingly this diagnosis is ruled out. Riedel's thyroiditis is also a possibility, but this is exceedingly rare.

DR. JOHN W. RAKER: The thyroid gland was explored under local anesthesia through a limited incision. It was possible to expose the anterior portion of both lobes and the isthmus and to palpate the entire gland. It was uniformly involved in a diffuse abnormal process. It was about twice the normal size, and many lobulations were present. It was firm and rubbery in consistence and grayish pink. The gross appearance seemed entirely consistent with chronic thyroiditis. A biopsy was obtained from a typical area in the left lower lobe.

CLINICAL DIAGNOSIS

Chronic thyroiditis.

DR. FARAHE MALOOF'S DIAGNOSES

Chronic thyroiditis; Hashimoto's type.
?Amyloid goiter.
Myxedema.
Rheumatoid arthritis.

ANATOMICAL DIAGNOSES

Chronic thyroiditis, Hashimoto's type (Hashimoto's struma).
(Rheumatoid arthritis.)

PATHOLOGICAL DISCUSSION

DR. WINFIELD S. MORGAN: Microscopically, the biopsy specimen showed a uniform picture consisting of the changes on which we usually base a diagnosis of the Hashimoto type of chronic thyroiditis. Although the lobular architecture was generally preserved there was extensive replacement of acinar parenchyma by lymphoid tissue, with germinal center formation (Fig. 1). The thyroid follicles were dispersed throughout the lymphoid stroma and were small, irregular and largely devoid of colloid. Most of the lumens contained lymphocytes or débris. Many of the epithelial elements consisted simply of small nests of cells with no visible lumen. In addition the thyroid cells were large and acidophilic and exhibited the nuclear pleomorphism commonly seen in this disease. The general character of their change was one of atrophy. There were no areas of normal or hyperplastic thyroid tissue in the biopsy specimen.

Although one may have some hesitation in making a diagnosis of Hashimoto's struma in a man, since all

FIGURE 1.

the cases described by Statland et al.[5] were in women, I believe that the combined weight of the clinical picture, the diffuse glandular enlargement, the findings at operation and the histologic picture gives adequate support to that diagnosis.

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IMPLICATIONS OF RETROLENTAL FIBROPLASIA

THE emergence of a new disease is indeed rare in the middle of the twentieth century, but during the last ten years a truly new problem has appeared in retrolental fibroplasia. The implications of its recognition, progression and prevention are not confined to the new disease: they promise much for clarification and control of some of the oldest conditions of which there is historical record, the congenital deformities.

The very success of contemporary effort in conserving the lives of prematurely born babies has contributed to the development of other problems, sharply brought into focus by a significant increase of blind people in the population. First described by Terry in 1942, retrolental fibroplasia has accounted in late years for nearly two thirds of the admissions to institutions for the visually handicapped. The disease could not have been widely prevalent before 1940 since the late visual manifestations — often total blindness — are so pronounced that eventual recognition of the severe defect is inevitable. First manifestations are observed on ophthalmoscopic examination at six to eight weeks of age, with engorgement and tortuosity of retinal vessels, and are followed by the penetration of neovascular tissue into the vitreous and ultimately by detachment of the retina and formation of a grayish membrane in the retrolental space. The condition is clearly related to prematurity and fetal development, for the premature infant is no less a fetus simply because it is no longer contained by its mother. It is vulnerable when it reaches the stage that is critical for retinal vascularization. The premature precipitation of an immature fetus into an extrauterine world brings real hazards, many of which, but not all, have been controlled in the modern premature nursery by regulation of the infant's fluid and food requirements, attention to respiratory difficulties and increasing use of oxygen at relatively constant temperature and humidity for many days and weeks.

Ever since retrolental fibroplasia was first linked with prematurity and then with the growth of premature infants in incubators, almost every aspect of the medical regimen has been suspected of influencing pathogenesis of the disease. Most of these suspect factors have been exonerated too soon, for seemingly harmless circumstantials of development may exert their effects synergistically. Oxygen, which offers so much in the way of counteracting asphyxia when there is a clear indication, has recently received intensive study as being solely to blame, but Ingalls and Purshottam, elsewhere in this issue of the *Journal*, view oxygen, whether in excess or in greatly reduced amounts, as primarily responsible and point out its possible connection with secondary factors. Temperature, humidity, hemoconcentrations, electrolytic and enzyme derangements are thought to influence the development of retrolental fibroplasia and also to apply to the broad biologic problem of congenital anomalies.

The present paradox of increasing visual disability as the instruments for saving life are perfected has vividly brought out the multiple facets of pathogenesis and the fallacy of the search for a single cause. Various investigators have made it increasingly clear that many factors enter into the causative complex; a better understanding of how they interfere with the normal course of development may throw considerable light on abnormal processes that take place when the fetus is younger and more fragile still, when it is an embryo only and when aberrancy leads to congenital deformity as the term is conventionally understood. The solution of the problem in its entirety will only come when the pathogenesis, etiology and epidemiology are recognized as a collaborative challenge to workers from many disciplines and interests. The contributions of the embryologist, physiologist, anat-

omist, biochemist, ophthalmologist, pediatrician, obstetrician, statistician and epidemiologist are all apparent in the progress so far attained.

CERTIFIED MILK

THE sale of the Walker-Gordon farm in Charles River Village last autumn removed from the field of certified-milk production in New England a name long associated with this specialized branch of the dairying industry.

Originating some sixty years ago, the regular inspection and certification of selected farms by medical milk commissions has been partly responsible for the gradual revolution that has taken place in dairying methods in general. The role of certification in this revolution has been twofold. It has been responsible for the actual production of a nearly clean and almost safe raw milk, in an era when most milk was raw, dirty and unsafe, and for the development of methods and standards of production that others might emulate.

Nor has certification been entirely static over this period. Concerned originally with the sanitary domiciling of milking cows and matters of personal bovine toilet, to which were joined tuberculin testing, bacterial counts, determination of butter fat and milk solids and the inspection of milk handlers, it has progressed to a standardization of vitamin content and as a crowning achievement in many areas the final pasteurization of the product.

Of late years, however, with pasteurization of all grades of milk becoming mandatory in urban areas and a degree of uniformity of farm inspection, the importance of certified milk has declined. Whereas some years ago at least nine farms were simultaneously certified by the Boston Medical Milk Commission, the recent sale of the Walker-Gordon farm reduced the number to two. This decreased the number of milking cows under the oversight of the Commission from 869 in March, 1953, to 497 in October, and the amount of milk produced under its standards from 435,793 quarts in March to 205,518 in October.

Filling an original need as the only relatively safe food for infants, other than that emanating from the maternal fount, certified milk now serves another purpose. For its chief sale at present is as skim milk — a sale that amounted to 60 per cent of the total in 1952 and 66 per cent in 1953.

The secretary of the Boston Commission presented in his report for 1953 some pertinent questions that concern certified milk, at least in New England. Has certified milk a future or has its mission been accomplished? The factor bearing most heavily on this problematical future is the economic one, since Grade A milk has for some time been of such quality that any considerable price differential, as now exists, must eventually drive the higher-priced product from the market.

Are some of the requirements for certification unnecessarily high under modern conditions, and consequently are some of the expenses of producing certified milk unnecessary? Might the supervision of production be left in the hands of health departments, avoiding duplication of procedures by sanitarians and laboratories in the employ of the commissions? Is the weekly visit to a farm by a physician for the inspection of personnel of any real value now that milk-borne human infections are so much less a danger than they were twenty-five years ago? Are some of the other expensive medical procedures, such as stool examination for organisms of the typhoid group, still needed in New England as a routine measure?

Perhaps by further modernizing and streamlining of its technics certification may be brought to a point where certified milk can compete economically with milk of lower grade but of comparable safety. In no other way immediately discernible can its future be made to appear at all hopeful.

THE DISTRIBUTION OF PHYSICIANS

DURING World War II there was certainly a shortage of civilian physicians, as there were shortages of everything else from textbooks to taxicabs. Just when and how that wartime shortage was relieved is now hidden in the recollection of sustained political agitation for more doctors, more opportunities for "the poor boy," more medical schools and more federal support for medical education and research. The prescription for these ingredients of a universal panacea varied from one locality to another; in Massachusetts the formulas were altered radically after the ballots were counted in 1952. But even before the election it had been generally agreed that there was not a shortage so much as a maldistribution of doctors between the larger and the smaller centers of population.

It now appears that the distribution of physicians in the United States is extraordinarily good, according to Frank G. Dickinson, Ph.D., director of the American Medical Association Bureau of Medical Economic Research, who made a preliminary report at the fiftieth annual Congress on Medical Education and Licensure. Dr. Dickinson's study was based on a division of the country into 757 trading areas. He reported that every town with a population of more than 5000 had at least one physician in active practice, as had 96 per cent of those with a population between 2500 and 5000; 88.3 per cent of those with a population between 1000 and 2500, and 21 per cent of those with a population between 100 and 1000. More than half the latter group had less than 250 inhabitants. Only one sixth of 1 per cent of the population lived outside a 25-mile radius of the nearest

town with a physician in active practice. The title of Dr. Dickinson's report is "How Bad Is the Distribution of Physicians?" He has asked a good rhetorical question.

DR. FOWLER AND THE AMERICAN ACADEMY OF GENERAL PRACTICE

THE national honors that befall Massachusetts physicians are many and varied, the latest being the election of Dr. John R. Fowler, of Barre, as president-elect of the American Academy of General Practice, at the sixth annual meeting in Cleveland, March 22-25.

The election of Dr. Fowler to this high position in what is now the third largest of American medical societies is not only an honor for Massachusetts and the Massachusetts Medical Society, of which he is an active member, but also a reflection of the esteem in which he is held by his fellow general practitioners, for whose cause he has been working untiringly.

The *Journal* extends its congratulations to Dr. Fowler, wishing him the same success with the American Academy that he experienced as the first president of the Massachusetts Academy of General Practice, which grew in size and prestige under his capable guidance.

Dr. G. C. Hebbe has been appointed U. S. Consul to Aix la Chapelle. He is a foreigner, sent home to represent a country of which he knows but little.

Boston M. & S. J., *April 19, 1854*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

NEIL—Richard J. Neil, M.D., of Methuen, died on March 17. He was in his fifty-first year.

Dr. Neil received his degree from Tufts College Medical School in 1930. He was senior obstetrician and gynecologist, Lawrence General and Bon Secours hospitals, consulting obstetrician and gynecologist, Clover Hill Hospital, medical adviser. Red Cross Blood Procurement Program, and formerly school physician, Methuen, a member of the Council of the Massachusetts Medical Society and censor of the Essex North District Medical Society. He was a fellow of the American Medical Association and a member of the New England Obstetrical and Gynecological Society.

He is survived by his widow, a daughter, a son, his mother, two sisters and several nieces and nephews.

CORRESPONDENCE

REVOCATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held on March 25, 1954, the registration to practice medicine of Dr. Michael Litvich, 640 Boulevard, Revere, was revoked.

ROBERT C. COCHRANE, M.D., *Secretary*
State House
Boston

BOOK REVIEWS

The Heart Beat: Graphic methods in the study of the cardiac patient. By Aldo A. Luisada, M.D. 4°, cloth, 527 pp., with 311 illustrations. New York: Paul B. Hoeber, Incorporated, 1953. $12.00.

Dr. Luisada has long been interested in the graphic recording of cardiovascular activity. This book brings up to date the information accumulated since the publication of Sir Thomas Lewis's *Mechanism and Graphic Registration of the Heart Beat*, and thus fills a reference need. There is no attempt to furnish complete bibliographies of any special technic, particularly of the older methods such as phonocardiography, electrocardiography and roentgenology. The catalogue of other available recording technics is impressive — cardiography, epigastric cardiography, ballistocardiography, phlebography, hepatography, esophagocardiography, internal pneumocardiography, pleural tracings, aortography, carotid and subclavian sphygmography, peripheral sphygmography, phonoarteriography, phonophlebography, plethysmography, graphic sphygmomanometry and phlebomanometry, cardiomanometry, roentgenkymography, electrokymography, rheocardiography, radiocardiography, pneumography, pneumotachography, electrobronchography, and spirography.

Descriptions of these methods is followed by a section on the electric phenomena of the heart and vessels, and discussions of physiologic variants of the graphic tracings, clinical applications of graphic methods and descriptions of apparatus.

Although it is justifiable to limit the space allotted to commonly used methods, fully discussed in special books, it leads to an overemphasis on some of the less valuable procedures. For example, 8 pages are devoted to cardiac catheterization and 27 pages to electrokymography — a technic of particular interest to the author, who states that the electrokymogram is of "primary importance" for the diagnosis of mitral insufficiency. This conclusion is not shared by others who have tried the method, and, as recently reported by Davison and Epps in the *British Heart Journal* (16:49, 1954), "The left auricular electrokymogram proved valueless as a means of differentiating between pure mitral stenosis and mitral stenosis with incompetence."

It is useful to have a volume describing the ways in which various mechanical, vibrational and electric activities of the cardiovascular system have been recorded. The fact that such tracings can be made need not imply that they are always of value.

HOWARD B. SPRAGUE, M.D.

Diagnostic Electroencephalography. By Hans Strauss, M.D., Mortimer Ostow, M.D., Med.Sc.D., and Louis Greenstein, M.D. 4°, cloth, 282 pp., with 46 illustrations. New York: Grune and Stratton, 1952. $7.75.

This book describes the appearance of the electroencephalographic record in terms of the voltage, frequency and distribution of waves under normal and abnormal conditions. The major part of the volume is a catalogue, and discussion of the frequency with which certain normal and abnormal patterns resulted from having various diseases of the brain, epilepsy and diseases of other parts of the body,

the influence of drugs, hormones and certain chemical agents and psychiatric diseases. The observations of others are compared briefly. About 40 records are reproduced in reduced size. The extensive bibliography goes little beyond 1949. There is a good index.

WILLIAM H. TIMBERLAKE, M.D.

A Source-book of Medical Terms. By Edmund C. Jaeger, D.Sc. With a foreword by Irvine H. Page, M.D. 8°, cloth, 145 pp., with illustrations by Lloyd M. Smith and the author. Springfield, Illinois: Charles C Thomas, 1953. $5.50.

In this small book the author presents in alphabetical form the various word elements from which medical terms were formed. The original words in Greek, Latin, French and other languages from which the elements were derived are given with their meanings. Special emphasis is given to prefixes and suffixes. Certain terms are placed in boxes, and expanded definitions of these words are given. An interesting example is the old Greek term for a kind of beak, curved, crow or raven, that was Latinized into corona, a crown, and corax, the raven. Anything that resembled a crow's beak became a natural in the evolution of words — hence the anatomic terms, coracoid and coranoid processes.

This small book is a worthy complement to the monumental medical dictionary of Foster (Philadelphia: D. Appleton and Company, 1890-1894), which gives the Greek and Latin derivations and their equivalents in modern languages and their definitions in English. Taken together, these two works form an invaluable source of medical terminology.

JAMES F. BALLARD

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Lesions of the Lumbar Intervertebral Disc: With special reference to rupture of the annulus fibrosus with herniation of the nucleus pulposus. By R. Glen Spurling, M.D., clinical professor of surgery (neurosurgery), University of Louisville School of Medicine. 8°, cloth, 148 pp., with 45 illustrations. Springfield, Illinois: Charles C Thomas, 1953. $4.75. (Publication No. 177, *American Lecture Series.*)

The author of this special monograph discusses all aspects of lesions of the intervertebral disk, as well as its anatomy, physiology, pathology, diagnosis and treatment. A short historical sketch precedes the text proper. The literature has been surveyed, and there is a bibliography of 7 pages. There are indexes of subjects and authors. The book should be in all medical libraries and in the collections of orthopedists.

The Hypertensive Disorders of Pregnancy. By Ernest W. Page, M.D., associate professor of obstetrics and gynecology, University of California School of Medicine, San Francisco. 8°, cloth, 120 pp. Springfield, Illinois: Charles C Thomas, 1953. $3.75. (Publication No. 188, *American Lecture Series.)*

Dr. Page, in this small monograph, discusses the clinical aspects, the physiologic and biochemical changes in normal pregnancy and in toxemia, and the etiology of toxemia. The literature is surveyed, and there is a bibliography of 145 references. The small book should be in all obstetric collections.

Mother and Baby Care in Pictures. By Louise Zabriskie, R.N., director, Maternity Consultation Service, New York City. Fourth edition. 8°, cloth, 244 pp., with 255 illustrations and 11 tables. Philadelphia: J. B. Lippincott Company, 1953. $3.00.

This new edition of a popular book has been completely rewritten, reorganized, revised and brought up to date. Much material and many pictures have been added.

Handbook of Practical Bacteriology: A guide to bacteriological laboratory work. By T. J. Mackie, C.B.E., M.D., LL.D., D.P.H., professor of bacteriology, University of Edinburgh, consultant bacteriologist to the Royal Infirmary, Edinburgh, and the South-Eastern Regional Hospital Board, Scotland; and J. E. McCartney, M.D. (Edin. and Adelaide), D.Sc. (Edin.), medical bacteriologist, Institute of Medical and Veterinary Science, Adelaide, South Australia. Ninth edition. 8°, cloth, 677 pp. Edinburgh: E. and S. Livingstone, Limited, 1953. $5.50. (Distributed by Williams and Wilkins, Baltimore.)

This standard English handbook has been revised and brought up to date. First published in 1925, it has gone through 9 editions and 12 printings. There is an extensive index; the printing was done in Great Britain, and the publishing is excellent.

Female Sexuality. By Marie Bonaparte. 8°, cloth, 225 pp. New York: International Universities Press, Incorporated, 1953. $4.50.

The author has divided her text into three main parts: bisexuality in woman; the erotic function, a biophysic function; and evolutionary perspectives (which also deals with passivity, masochism and femininity, some palaeobiologic and biopsychical reflections and notes on excision [clitoridectomy]). There is a short bibliography and an index.

Salmonellae and Shigellae: Laboratory diagnosis correlated with clinical manifestations and epidemiology. By Alfred J. Weil, M.D., Department of Bacteriology, Bronx Hospital, New York City; and Ivan Saphra, M.D., Department of Bacteriology, Beth Israel Hospital, New York City. 8°, cloth, 247 pp., with 14 illustrations and 35 tables. Springfield, Illinois: Charles C Thomas, 1953. $7.75.

This is a comprehensive manual dealing with the bacteriologic and clinical aspects of the two groups of organisms. The pertinent literature has been noted, and there is a bibliography of 10 pages and a good index. This book should be in all medical libraries and clinical laboratories.

An Approach to General Practice. By R. J. F. H. Pinsent, M.A., M.D. (Cantab.). With a foreword by Sir Lionel Whitby, C.V.O., M.C., Regius Professor of Physic, University of Cambridge. 8°, cloth, 166 pp. Edinburgh: E. and S. Livingstone, Limited, 1953. $3.50. (Distributed by Williams and Wilkins, Baltimore.)

Dr. Pinsent discusses the conduct of a large general practice based on the experience gained from the treatment of 3000 patients in the large city of Birmingham, England, and the philosophy of illness as applied to the practice of medicine. The book should be available to general practitioners and in collections on general medicine.

NOTICES

NATIONAL TUBERCULOSIS ASSOCIATION

The fiftieth-anniversary meeting of the National Tuberculosis Association will be held in conjunction with the meetings of the American Trudeau Society and the National Conference of Tuberculosis Workers, at Atlantic City, May 17 to 23. The theme of the golden anniversary will be "The Challenge of the Future."

HOWE LECTURE ON OPHTHALMOLOGY

The Howe Lecture, under the auspices of the Howe Laboratory of Ophthalmology, Harvard Medical School and Massachusetts Eye and Ear Infirmary, will be given by Dr. Frank B. Walsh, associate professor of ophthalmology, Johns Hopkins University School of Medicine, and visiting lecturer in ophthalmology, Harvard Medical School, in Amphitheater D, Harvard Medical School, on April 20 at 5 p.m. The subject will be "A Clinical Study of Several Third-Nerve Lesions." All interested persons are invited.

CIVIL DEFENSE EXERCISE

The eighth command-post exercise of the Civil Defense Agency, Commonwealth of Massachusetts, will be held on May 3 from 7:30-9:30 p.m.

NEW ENGLAND MEDICAL CENTER HOUSE OFFICERS' ASSOCIATION

The annual Joseph H. Pratt Lecture of the New England Center Hospital will be delivered by Dr. J. Burns Amberson, professor of medicine, Columbia University College of Physicians and Surgeons, in Stearns Auditorium, New England Center Hospital, on April 28 at 7 p.m. The topic will be "Some Experiences in the Treatment of Tuberculosis." All interested persons are invited.

SOCIETY MEETINGS AND CONFERENCES

April 20. Howe Lecture on Ophthalmology, Page 663.
April 20. South End Medical Club. Page 585, issue of April 1.
April 20. Boston City Hospital House Officers' Association. Page 265, issue of February 11.
April 20–28. Consultation Clinics for Crippled Children. Page 490, issue of March 18.
April 21. New England Oto-Laryngological Society. Page 620, issue of April 8.
April 21. New England Deaconess Hospital. Thoracic Conference. Page 620, issue of April 8.
April 21. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.
April 21–24. Seminar and Conference on Cancer Cytology. Page 346, issue of February 25.
April 23–May 21. Boston Lying-in Hospital Journal Club. Page 38, issue of January 7.
April 24. Boston City Hospital Alumni Association. Page 491, issue of March 18.
April 24. Massachusetts Association of Medical Technologists. Page 540, issue of March 25.
April 26. Massachusetts Heart Association. Kidney Section. Page 585, issue of April 1.
April 26–May 2. International College of Surgeons. Page 492, issue of March 18.
April 27. Hampden District Medical Society. Page 620, issue of April 8.
April 28. Massachusetts Society of Examining Physicians. Page 585, issue of April 1.
April 28. Middlesex South District Medical Society. Page 585, issue of April 1.
April 28. New England Medical Center House Officers' Association. Page 664.
April 29 and 30. New York Academy of Medicine. Eastern States Health-Education Conference. Page 491, issue of March 18.
April 29, 30 and May 1. American Goiter Association. Hotel Somerset, Boston.
April 29, 30 and May 3–7. Yale University Silliman Lectures. Page 585, issue of April 1.
May 1. State University College of Medicine at New York City. Alumni Association. Page 400, issue of March 4.
May 3. Civil Defense Exercise. Page 664.
May 10–12. Institute of Industrial Health. Page 491, issue of March 18.
May 12. Middlesex East District Medical Society. Annual Meeting. (Harlow Dinner.)
May 12. Essex North District Medical Society Meeting. Andover Country Club, Andover.
May 12. New England Obstetrical and Gynecological Society. Spring Meeting. Longmeadow Country Club, Springfield.
May 14–16. Fifth Annual International Group of Doctors in Alcoholics Anonymous. Page 1004, issue of December 10.
May 14–16. American Academy of Dental Medicine. Page 38, issue of January 7.
May 15. Massachusetts Hospital School. Orthopedic Rounds. Page 265, issue of February 11.
May 17–21. National Tuberculosis Association. Page 663.
May 27–29. American College of Cardiology. Page 585, issue of April 1.
May 27 and 28. New York Surgical Division of International College of Surgeons. Page 585, issue of April 1.
May 31–June 3. American Urological Association. Page xvii, issue of July 23.
June 5 and 6. International Association for the Study of the Bronchi. Page 400, issue of March 4.
June 13–17. American Society of Medical Technologists. Page 444, issue of March 11.
June 14–16. American Neurological Association. Page 540, issue of March 25.
June 15–18. Medical Library Association. Page 491, issue of March 18.
June 17–19. American Geriatrics Society. Page 266, issue of February 11.
June 17–21. Pan American Congress of Ophthalmology. Page 540, issue of March 25.
June 19 and 20. Society for Investigative Dermatology. Page 540, issue of March 25.
June 23. Tufts Medical Alumni AMA Dinner. Page 585, issue of April 1.
July 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.
July 23–29. International Cancer Congress. Page 914, issue of November 26.
July 26–31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.
September 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.
September 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.
September 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.
September 16–18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.
October 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.
June 21–25, 1955. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, APRIL 22

THURSDAY, APRIL 22

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Thoracic Conference. Resection vs. Thoracoplasty in Pulmonary Tuberculosis. Dr. John Petter. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. The Differentiation Between Cardiac and Pulmonary Dyspnea. Dr. Laurence B. Ellis, Stearns Auditorium, New England Center Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, APRIL 23

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium. New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00 p.m. Boston Lying-in Hospital Journal Club. Boston Lying-in Hospital Auditorium, 221 Longwood Avenue.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill C. Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.
*5:00 p.m. Metabolism of Stable and Radioactive Metals. Dr. Daniel Laszlo. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

SATURDAY, APRIL 24

Massachusetts Association of Medical Technologists. Hotel Somerset, Boston.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
9:00 a.m. Boston City Hospital Alumni Association. Medical. Dr. John P. Rattigan. Cheever Amphitheater. Surgical. Dr. John J. Byrne. Amphitheater, Mallory Institute of Pathology. Orthopedic. Dr. Augustine W. Eddy. Shortell Unit, Boston City Hospital.
*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.
*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Auditorium, New England Center Hospital.

MONDAY, APRIL 26

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater. Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.